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THE MEDICAL CLINICS OF NORTH AMERICA

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LESIONS OF THE UTERINE CERVIX

MONTE C PIPER

The uterine cervix may be divided into two parts (1) the vaginal portion or portio vaginalis, which protrudes into the vagina, and (2) the supravaginal portion, or portio supravaginalis, which extends upward to the isthmus of the uterus The vaginal portion is composed of muscular, fibrous, and elastic bands and is covered with stratified squamous or pavement like epithelial cells The squamous epithelium is a continuation of that which covers the mucous membrane of the vagina It terminates at the external os The supravaginal portion is attached anteriorly to the bladder by bands of fibrous tissue These bands also extend laterally on either side into the parametrium Uterine arteries and nerves, the ureters, and the lymphatic structures which are contained in these bands of connective tissue are situated within 2 cm of the cervix, on either side The posterior part of the supravaginal portion is covered by the peritoneum of the cul-de-sac

The cervix is relatively insensitive to pain such as that which usually is produced by the cautery but it is sensitive to stretching or forceful dilatation

The cervical canal is fusiform in shape and is about 2 5 cm in length The mucosa contains branched or racemose glands These glands are lined with columnar epithelial cells, which contain a basally placed nucleus and a clear cytoplasm The columnar cells which line the glands of the endometrium

have a central nucleus and granular cytoplasm The columnar cells of the cervical canal terminate at the external os, where they join the stratified squamous or pavement epithelium There is a tenacious, mucous secretion in the cervical canal This is slightly alkaline in reaction and normally is sterile, the cervical canal normally is sterile The vaginal secretions are acid and contain the bacterial flora of the vagina The Bacillus doderleini assists in maintaining the acidity of the vaginal secretions There is a longitudinal ridge on the anterior and posterior walls within the cervix These ridges give off oblique folds (palmate folds), which interlock and tend to keep the cervical canal closed

Benign lesions of the cervix seem to suggest a field of prophylaxis in malignant disease of the cervix In a large majority of cases of malignant disease of the cervix, the disease appears to follow trauma or chronic infection, such as results from childbirth or instrumentation, and which causes cervicitis Carcinoma of the cervix affects multiparas more frequently than it affects nulliparas

The great majority of deliveries are accompanied by some laceration of the cervix In some cases the laceration may appear to be too small to be significant, but in cases in which manual assistance has been necessary, the resulting laceration of the cervix may be extensive The cervix is situated in a pouch in the posterior vaginal vault, and the secretions which are contained in the pouch bathe the cervix Inasmuch as the lochia is not sterile after the third day after delivery, the injured cervix is bathed constantly with infectious material

The question of early repair of all lacerations of the cervix has been a source of contention Since some of the most severe lacerations occur in cases in which the patients are delivered in their homes, convenient facilities for cervical repair seldom are available The procedure, therefore, presents serious difficulties

Erosion, eversion, ectropion, and nabothian cysts may follow an infected laceration of the cervix These changes are evi-

dence of the chronicity of the lesion Strachan has expressed the opinion that the inflammatory after effects of trauma are more persistent in the uterine cervix than they are in any other organ in the body Eversion of the cervix is an outpouching of the overgrowth of tissue which has piled up in the cervical canal Ectropion of the cervix is an exaggerated eversion, which is caused by laceration and retraction of the circular, muscular, fibrous, and elastic fibers of the cervix. Nabothian cysts are small mucous cysts which occur when the nabothian follicles are sealed or compressed by squamous or columnar epithelium Erosion is the most frequent pathologic change which follows laceration of the cervix It is the result of the effort of the columnar and squamous epithelium to cover the raw, infected edges of the lacerated cervix

The organisms which most frequently cause cervicitis are the streptococcus, staphylococcus, Neisseria gonorrhœæ, and Escherichia coli Leukorrhea is the most common symptom of cervicitis Edema of the cervix, which interferes with the blood supply and the normal muscular motility, may cause faulty involution of the uterus and some disturbance of menstruation Sacral and lumbosacral backache are present in about 45 per cent of these cases Sterility may be the result of the abnormal secretion and plugging of the cervical canal Severe erosions may be responsible for spotting after coitus An infected cervix may be considered a focus of infection Strumdorf has referred to the cervical mucosa as the "tonsil of the uterus"

Many women tolerate profuse leukorrhea and severe infection of the cervix for years because they believe that these conditions are a part of their lot If they could visualize the cervix, they would not rest until the condition had been treated and had healed Miller, Martinez and Hodgdon have reported that 80 per cent of multiparas and 10 per cent of primiparas have erosion of the cervix of varying degree Although the observation of other investigators vary it is likely that 50 per cent of multiparas have cervical lesions Barrett has reported that at the Woman's Hospital (New York), all

lacerations of 1 cm or more are sutured immediately, unless there are contraindications such as shock or infection All patients are observed in the follow-up clinic for six or eight weeks At the end of six weeks, Barrett found good involution of the uterus and healing of the cervix in about half of the cases A focus of infection in the cervix may be responsible for various systemic symptoms Langstroth has said that "focal infection of the cervix is second to no other as a factor in the cause of systemic, mental and nervous manifestations and diseases" There are some cases of scleritis and similar infectious diseases of the eye, in which the condition seems to improve after the infection of the cervix has been eradicated When the racemose glands become infected, there is round-cell infiltration in the subepithelial tissue The genital organs are richly supplied with blood vessels and lymphatics, which may readily spread the infection throughout the body

It is probable that erosion is the result of repeated efforts at spontaneous healing Sexual trauma or other injuries partially tear down the piled-up columnar or squamous epithelium and allow repeated infection of the cervix An erosion is evidence of chronicity of the lesion It is likely to persist until after the menopause After menopausal atrophy, there is a diminished blood supply to the uterus and cervix, and malignant changes in the cervix become more frequent than before

In 71 8 per cent of a series of 990 cases in which the cervix of the uterus was cauterized for benign lesions at the clinic during 1926, 1927, and 1928, the patients were between the ages of thirty and fifty years Of the patients who belonged to this age group, 82 1 per cent had had children and 17 9 per cent had not

The incidence of malignant disease of the cervix has been expressed rather clearly by Hirst, who said that carcinoma eventually will develop in some part of the body of one out of every eight women who attain the age of thirty-five years He also said that 25 8 per cent of these carcinomas would be situated in the genital tract, and that 80 per cent of the carcinomas of the genital tract would involve the uterine cervix

This author also reported that in one out of every four cases of carcinoma of the cervix, there was a chance for cure which would last for more than five years, but that three out of every four patients who have carcinoma of the cervix will die within five years, in spite of the best known means of treatment at the present time Of course, the patient who may survive for more than five years is the one who has a growth which is confined entirely to the cervix and which has not extended to adjacent tissues or metastasized to the lymph nodes Although the incidence of carcinoma seems to have increased definitely in the past thirty five years, the percentage of cures has not improved materially Improvement in the treatment of carcinoma of the cervix would appear to depend on some possible method that would permit the malignant nature of the lesion to be recognized earlier than it is at present, and on preventive measures Careful yearly examination undoubtedly would result in the early recognition of many of these growths The cervix of a woman who has borne children, or the cervix which previously has been the site of a lesion, should be examined more carefully and more frequently than is the common practice Such diagnostic procedures as staining the cervix with compound solution of iodine, as described by Schiller, and the use of the colposcope of Hinselmann for the early detection of areas of leukoplakia have been tried by many gynecologists but their value is uncertain It would seem that treatment of all erosions and similar benign lesions of the cervix, which is instituted promptly and continued until the lesions are healed, would constitute a very valuable preventive measure

Dr Wilder Hirst's figures for the incidence of carcinoma are very interesting they make the condition seem more horrible than it really is

Dr Piper These figures refer only to women who are past the age of thirty five years They are not necessarily mortality figures Holden has said For many years it has been the author's practice to treat routinely every lacerated infected cervix with tincture of iodine regardless of how small the lesion may be or whether or not any symptoms are present

In a large series so treated over a period of many years the author has never seen cervical carcinoma develop Dickinson, who has pursued a similar course, has had the same results" Hunner reported 2,895 cases in which cervicitis was treated with the cautery or amputation Carcinoma had not developed in any of these cases ten years after the operation

Some authorities believe that carcinoma of the cervix develops on a basis of chronic cervicitis and that early eradication of chronic disease of the cervix constitutes a definite means of prophylaxis in the prevention of carcinoma

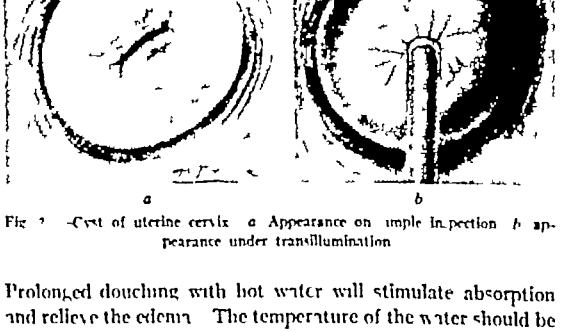
Carcinoma frequently develops in a diseased cervical stump after hysterectomy Johnson and Tyrone reported ten cases of carcinoma of the cervix in which the cervix previously had been cauterized or subjected to a plastic operation They also reported twenty-one cases in which carcinoma of the cervical stump followed abdominal hysterectomy Nine hundred ninety patients who had benign lesions of the cervix were treated by cauterizing the cervix at the clinic, in 1926, 1927, and 1928 It was possible to trace 640, or 64 6 per cent, of these patients Only one of these patients reported the carcinoma had developed in the cervix, subsequent to cauterization This patient had a cervical polyp which had been removed in 1927 The base of the polyp had been cauterized In August, 1931, carcinoma of the cervix had been treated elsewhere with radium, and hysterectomy had been performed in February, 1932 The patient was still living in August, 1934

Dr Mussey I occasionally have used Schiller's test but it does not appear to be pathognomonic There are cases of simple erosion of the cervix in which staining with compound solution of iodine does not take place I therefore feel that, in cases in which carcinoma of the cervix is suspected, it is much better to secure biopsy than it is to depend on Schiller's test

Dr Piper In cases in which there is doubt, it seems much safer to rely on biopsy than to depend on Schiller's test Several specimens may be obtained for biopsy These may be

sent directly to the laboratory A good light is essential and the cervix should be well exposed with the speculum The cervix should be wiped clean with cotton tipped applicators If the little "cold" light is inserted into the cervical canal, the transillumination may disclose unsuspected cysts (Fig 27) and areas of scar tissue

Every physician probably has a pet method which has proved satisfactory in the treatment of cervicitis There are many different methods of treatment and each has some good points When compared to the use of the cautery, the employment of other methods of treatment seems to be temporizing



a *b*

Fig 7 —Cyst of uterine cervix *a* Appearance on simple inspection *b* appearance under transillumination

Prolonged douching with hot water will stimulate absorption and relieve the edema The temperature of the water should be about 112° F , and about 2 gallons (8 liters) should be allowed to flow slowly through the vagina The Elliott heat treatment, as the result of pressure and heat, produces a milking out process and reduces the extent of the involvement This treatment also is useful in cases in which the adnexa are involved It may be used either before cauterization, especially in cases in which the inflammation is too acute to permit the cautery to be employed or after cauterization, in cases in which the cauterized tissue has partially healed At the clinic,

we have started to use the Elliott treatment three or four days after cauterization and have employed it daily thereafter, and have not seen any unfavorable results from its use

Cauterization with the nasal tip applicator can be done in the office, and thereby saves the patient the expense of hospitalization and charges for the operating room The procedure requires but a few minutes and the patient remains ambulatory A local anesthetic is seldom required, even if the tissue to be cauterized is rather extensive The apparatus is inexpensive and the application is simple At the clinic, we usually cauterize the entire cervix at one time Some physicians prefer to cauterize only a portion of the cervix at the first treatment and to continue the cauterization about ten days later It has not seemed necessary to prolong the treatment in this manner We do, however, ask the patient to return about every second day for ten to fourteen days At these visits, the loosened slough is wiped off and the cervical canal is cleansed of debris The latter procedure possibly may be a factor in the prevention of stenosis Before cauterization, it is advisable to map out mentally the area to be cauterized If both lips of the cervix are involved, the lower lip should be treated first and the upper lip should be treated next All cysts should be destroyed completely with the cautery Finally, the applicator should be inserted into the cervical canal for a distance of 1 to 1 5 cm , in order to eradicate the endocervicitis During the last procedure, the patient may experience cramps, which are similar to menstrual pains, and a feeling of warmth in the vagina The latter is caused by the heat of the wires The patient does not complain very often of pain The application of a 10 per cent solution of cocaine seems to relieve some patients of any sense of discomfort The physician must be very careful not to allow the wire shank of the applicator to touch the wall of the vagina, which is very sensitive If a section of Penrose drain rubber tubing is placed over the speculum, it helps to retract the lateral walls of the vagina and prevents the shank of the applicator from touching the walls of the vagina

If the patient feels shaky after the cauterization has been completed, she should be allowed to lie down until she feels able to leave Slight bleeding occasionally occurs after the patient returns home but this usually ceases spontaneously if the patient lies down Occasionally, it may be necessary to insert a strip of sterile packing in the vagina or to touch a bleeding point with a dull red cautery tip, in order to stop the oozing of blood Severe hemorrhages may follow extensive or deep cauterization, which is employed in the hospital, but the bleeding seldom is severe after cauterization with the nasal tip loop in the office A profuse discharge, which has an offensive odor, appears in four to six days after cauterization and continues for seven to ten days, or until the slough has separated entirely At the end of six weeks, the tissue is well shrunken and healed It is well to inspect the result carefully after the tissue has healed Deep cysts may have been missed or a small erosion may have persisted

There has been very little evidence of stenosis, such as has been reported to follow the use of electrocoagulation or the use of chemical caustics At the clinic, we try to extend the cautery lines beyond the edges of the erosion and it is possible that the shrinkage which results from the formation of scar tissue tends to hold the cervical canal open and to prevent stenosis There does not seem to be any particular contraindication to the use of the cautery in the office, except the acuteness of the infectious process

Dr Mussey How does this process differ from electrocoagulation?

Dr Piper I have not used electrocoagulation Many physicians have reported favorable results with this procedure My impression is that there is more likelihood of stenosis after electrocoagulation of the cervix than there is after cauterization Electrocoagulation of the cervical canal is easier to accomplish than is electrocoagulation of the vaginal portion of the cervix With direct vision, it is possible to determine the depth and extent of cauterization that is required

Dr Barker I would like to know how to determine in

an individual case, whether the cervix should be cauterized in the office or in the hospital

Dr Piper This depends on the extent of the lesion If the laceration and chronic infection of the cervix are so extensive as to require virtually amputation of the cervix with the cautery, the surgeon is requested to perform the cauterization in the hospital An anesthetic usually is required in these cases If some other surgical procedure, such as curettage, is indicated, cauterization may be done advantageously at the same time However, cauterization of the cervix in the office may improve the pelvic disease sufficiently to aid necessary surgical operations to be performed subsequently

Dr Snell What is the effect of amputation of the cervix on future deliveries?

Dr Mussey In answer to Dr Snell's question, I might say that after high amputation of the cervix, we view subsequent pregnancies with much trepidation The cervix will not dilate, or if it does dilate, a laceration may extend into the broad ligaments and sometimes into the uterus I advise amputation of the cervix in cases in which no further childbearing is anticipated I prefer ordinary cauterization, or even deep cauterization, of the cervix in cases in which the patients are in the childbearing age The latter procedure does not seem to result in as much fibrous tissue as does high amputation

Dr Piper It might be of interest to mention a few of the results which were obtained in the 990 cases in which cauterization of the cervix was performed in 1926, 1927, and 1928 It was possible to trace 358, or 78 9 per cent of the 454 patients who had backache Of this group, 225, or 62 8 per cent, of the patients said that they had been relieved of the backache, and forty-one patients, or 11 4 per cent, said that the backache had been improved This was six years after the cauterization There were ninety-two patients, or 25 7 per cent, who said that the backache was unimproved

Dr Woltman What was the character of the backache in these cases?

Dr Piper It was of the sacral or lumbosacral type I

have seen cases in which the backache disappeared the day after the cauterization

Dr Brown Do you mean to convey the idea that the treatment of cervical erosions should be employed much more extensively than it has been in the past? If 100 women, who were in the childbearing age, had cervical erosions, which did not produce symptoms, what percentage would you consider it necessary to treat?

Dr Piper I would treat all who had an erosion of the cervix

Dr Brown You believe that every woman who has an erosion of the cervix should receive treatment?

Dr Piper Many times these women do not have any symptoms They should be treated because this constitutes a prophylactic measure against carcinoma of the cervix

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THE METRORRHAGIC TYPE OF FUNCTIONAL DISTURBANCE OF YOUNG WOMEN

DELLA G DRIPS

The metrorrhagic type of functional menstrual disturbance of young women is characterized by a tendency to more frequent, more profuse and more prolonged menses than is considered normal The periods of bleeding may continue constantly for weeks and even months There is almost always, in the truly functional case, a history of some irregularity of the menses from the onset of menstruation This is most often represented by short or long periods of bleeding occurring after short or long intervals It is assumed that the fault must be associated in some way with the functional development of either of the glands involved the anterior lobe of the pituitary or the ovaries The sterility which is common in this group of cases fosters this assumption

It is difficult for us, with the means at hand at present, to determine whether the dysfunction is primarily of pituitary or of ovarian origin When there is an associated tendency to obesity and no dysmenorrhea or exaggerated menstrual molimina or vasomotor disturbances such as hot flashes, we are inclined to feel that the disturbance is in the anterior lobe and *vice versa* The patients without symptoms, other than bleeding and sterility, are much in the majority, fortunately For with young women suffering with dysmenorrhea as well as with profuse and prolonged menstrual flow, the problem becomes very complicated The dysmenorrhea is usually of ovarian type, is present before and during the menses, and is likely to be very severe

Judging from the observations made in the examining room and at operation in these cases there seems to be a marked

tendency to the development of cystic follicles in the ovaries and to absence of normal corpora lutea The uterus is usually larger than normal and the endometrium, removed with the curet, is abundant and of the hyperplastic, polypoid type Examinations of the urine and blood, made to determine the quantitative amount of estrin or estrogenic hormone secreted by the ovaries, have revealed amounts above normal This seems to fit in with the clinical observations Cystic ovaries should produce more estrogenic hormone than normal ovaries and the result of overproduction of estrogenic hormone would be exaggeration of the size and turgor of the uterus and of the hyperplasia of the endometrium The luteal hormone is not produced in sufficient amounts, because of lack of formation of normal corpora lutea in the ovaries Therefore, the endometrium remains in the proliferative phase and does not go over into the normal premenstrual or pregravid secretory phase necessary for nidation of the ovum We have no way of knowing, as yet, how deficient the amount of luteal hormone may be, for it has not been identified outside of the corpus luteum Some sort of balance between the estrogenic and luteal hormones secreted by the ovaries seems to exist normally When the luteal hormone is deficient, the estrogenic hormone is apparently secreted in excess Very small amounts of luteal hormone seem to be able to affect this balance

Understanding of the physiology in these cases has helped greatly in establishing a sound basis for the treatment, and if treatment is initiated early and pursued with persistence and patience through the developmental years, often by the age of twenty-one to twenty-three years, a physiologic functional balance finally asserts itself

Before proceeding to the treatment, I wish to emphasize the necessity for ruling out any organic cause for the irregularity It is sometimes very difficult to rule out a blood dyscrasia Tumors or diseases of any of the endocrine glands must be eliminated It is necessary, therefore, in every case, to make complete studies of the blood, including flocculation tests, to examine the eyegrounds, and visual fields, to make

roentgenograms of the sella turcica, and to determine the basal metabolic rate The basal metabolic rate is, at times, lower than normal without any signs of myxedema being present This is thought to be associated with decreased function of the pituitary anterior lobe If the rate is low, thyroid extract is definitely indicated in the treatment and at times is sufficient to control the tendency to bleeding It is most difficult to rule out local pelvic pathologic conditions Small, submucous fibromyomas frequently produce a meno-metrorrhagia that is very difficult to identify Quantitative estimation of the urinary estrin may help here, for this substance is not present in more than normal proportions in these cases At times it is necessary to perform curettage for diagnosis Pelvic exploration may need to be resorted to in doubtful cases, to rule out ovarian neoplasms or endometrial tumors After establishing the diagnosis, the choice of treatment depends on the age of the patient, on the severity of the bleeding, and on the length of time since the onset of this

Considering the foregoing, the most conservative measures possible are always tried out first. Younger girls whose bleeding has not been severe, are given a diet especially high in vitamins, iron and calcium The normal weight of the patient should always be considered in outlining the diet If the girls cannot drink milk, calcium lactate is given in amounts of 1 drachm (4 c c.) dissolved in some hot liquid three times a day after meals Just how calcium helps is unknown Injections of parathyroid hormone, which raises the level of the blood calcium have been reported to be of help, temporarily at least, in checking the bleeding In addition to the foregoing, sistomensin is given by mouth, usually two tablets three times a day after meals This preparation contains some estrin, but is given in these cases for its content of active luteal hormone, which often is sufficient to check the flow For some years it has been the only effective preparation of luteal hormone available During periods of more profuse flow, I advise one or two ampules each day, given intramuscularly Recently I have been using proluton an active standardized

luteal hormone prepared by the Schering Corporation The ampule, or 1 c c, contains ½₅ K E (rabbit unit) This is too soon to be sure about the effective dose, 1 c c daily has been sufficient in some cases After the bleeding stops, I have the patient continue to take the luteal hormone for at least three weeks, in order to bring about a more normal endometrium before the next period, then administration is discontinued until another period comes on, when administration is resumed In cases of too frequent periods, this medication often will postpone the period and will establish a more normal interval Kaufman, in Germany, in 1932, reported twelve cases of severe uterine hemorrhage of so-called functional type, treated with luteal hormone, in which the bleeding was controlled within a few days Other treatment had been employed without avail If the bleeding has been present for months, there usually is such a thickening of the endometrium that nothing can effect a change in it, and it is better gently to curet it out, and then to attempt to build up a new endometrium with hormone therapy

If the patient is markedly anemic, she should have a transfusion of blood Theoretically, this should have a favorable influence on the bleeding, introducing some of the needed hormone Practically, in the truly functional cases, it does not help to check the bleeding, and when it does help, I am always suspicious that an unrecognized pathologic condition of the blood is present Aside from transfusion, I depend entirely on a diet high in vitamins and high in iron, to improve the anemia, for the giving of sufficient quantities of iron, in a form such as ferric ammonium citrate, in my experience increases the bleeding This can be given between periods but not with the period Severe hemorrhages in these cases fortunately are not the rule, and it is surprising how much and how long the patients can continue to menstruate without getting markedly anemic

Ordinary activity does not increase the bleeding, as the girls themselves usually will declare I feel that they should be allowed to carry on as much as possible Excitement and

competitive sports should be avoided Rest, in bed, ice applied to the lower part of the abdomen, and small amounts of ergot, in addition to the medication mentioned, frequently will soon control an increased amount of flow If the bleeding persists and other measures have failed, a small amount of radium is inserted into the uterus, the amount depending on the age of the patient For a patient aged eighteen years, 150 mg hrs are given and for a woman aged thirty years, 350 mg hrs Stacy and Mussey, in 1929, reported a series of cases in which radium was used They advised that the initial dose be small enough to preclude any possible injury to the ovaries, and that it be repeated several months later if necessary The effect of the radium may not be apparent until six weeks after its application After six weeks, menstruation usually ceases for two or three months, during which time the patient regains her strength and overcomes the anemia When the periods return they tend to be more regular and the duration and amount of flow are more nearly normal Other methods have been tried but none has been found more effective

In 1932 I reported 213 cases in which a diagnosis of the metrorrhagic type of functional irregularity had been made here in the clinic, and in which the patients had been followed for one year at least One hundred ten of the younger women, who had not had the metrorrhagic tendency for a long time, who had milder bleeding, and who had not been subjected to glandular therapy were given sistomensin and calcium lactate, in addition to general hygienic measures being prescribed Three of these were given thyroid in addition, and two young women were treated with thyroid only Of these 112 women seventy five were improved and remained in good condition for the year at least In thirty-one cases curettage only was performed I chose these particularly, to see what effect curettage alone would have Twenty three were still improved at the end of a year Thirty six had curettage followed by administration of sistomensin and calcium lactate and twenty seven were still in good condition at the end of the year It is evident that in a certain number of cases the foregoing therapy

leaves the patients unimproved These we elect to give small doses of intra-uterine radium We treated twenty-four of the 213 in this way Twenty-two were still in good condition at the end of the year In a few cases other methods were tried Of the total of 213 patients treated, 152 (71 per cent) were improved and remained in improved condition for one year at least There is room for betterment in treatment and I am hoping that we can effect this with the standardized, active, luteal hormone which is now available

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LESIONS OF THE SMALL BOWEL OTHER THAN PEPTIC ULCER

HOWARD R HARTMAN

Aside from its liability to peptic ulcers and related lesions, the small bowel, from the pylorus to the cecum, rarely is implicated when serious intra abdominal disease occurs Evidence of intrinsic disease in the small bowel is so seldom found at exploratory operation or necropsy that this portion of the alimentary canal is often forgotten in diagnosis It is difficult to examine by any known technic Most of the symptoms from its lesions are those resulting from late sequelae It has been called "the silent area of the abdomen" There is, then, little reason to wonder why the small bowel has been lacking in clinical interest Nevertheless it is essential to realize that the small bowel is not immune to disease

To determine just what lesions occur in the small bowel and the frequency of their occurrence a search was made of the files of The Mayo Clinic for the last five years Most of the lesions were reported in the surgical records some were listed in the records of necropsies others tabulated as having been diagnosed roentgenologically and a few had been diagnosed on clinical evidence but then only when it seemed indisputable After excluding duodenal ulcers, duodenitis with a probable relation hip to ulcer, and gastrojejunal ulcers, a formidable mass of material embracing 466 case histories remained available for study This number of cases compared with the total number of patients registered during the five year period indicated an extremely low incidence, but this exaggerated the infrequency of involvement of the small bowel for the total registration is only partially made up of persons who have

abdominal complaints The literature dealing with lesions of the small bowel is not barren All writers emphasize the fact that the small bowel is seldom involved by intrinsic disease Many theories are advanced as to why this should be, all of them need scrutiny before acceptance This paper does not purport to be a complete discussion of the diseases of the small bowel, but proposes, merely, a classification of the representative lesions and attempts to give a general idea of what the lesions are and where they are situated

The number of cases reported would have been greater if a motley array of cases of postoperative adhesions had been included Such adhesions may cause no dysfunction, however, they are capable of causing symptoms of partial or complete obstruction of the intestinal lumen, and they are often blamed for symptoms that cannot be diagnosed accurately and, consequently, are tactfully held behind that cloak of ignorance "adhesions" They cannot be regarded as intrinsic to the small bowel and this study has been simplified by omitting them

NEOPLASMS

There were fifty-two neoplasms in the cases studied, of which thirty-one were malignant and twenty-one benign Of the malignant neoplasms, twenty-two were carcinomas and nine, sarcomas

No segment of the small bowel, in these cases, escaped either carcinoma or sarcoma

Carcinoma is really rare in this silent area of the digestive tract Judd, in 1919, reported twenty-four cases of carcinoma of the small bowel, Rankin and Mayo, in 1930, added thirty-one more During the period in which these fifty-five cases of carcinoma of the small bowel were encountered, carcinoma of the large bowel, on the other hand, was found in 4,597 cases and carcinoma of the stomach, in 4,335 Since the report of Rankin and Mayo, fifteen additional cases of carcinoma of the small bowel have been observed at the clinic Thus, to date, there are but seventy cases of carcinoma of the small bowel recorded in the files of The Mayo Clinic Among the twenty-

two cases in the present report, seven occurred in 1929 and were included in Rankin and Mayo's series

When it is known that the patient has primary carcinoma in some part of the gastro-intestinal tract there is only one chance in more than 160 that it is in the small bowel It is remarkable how the small bowel seems to be partially immune to spontaneous malignant involvement as well as to invasion by malignancy Even when the pathologist is willing to admit that in a given case the carcinoma may be primary in the duo-

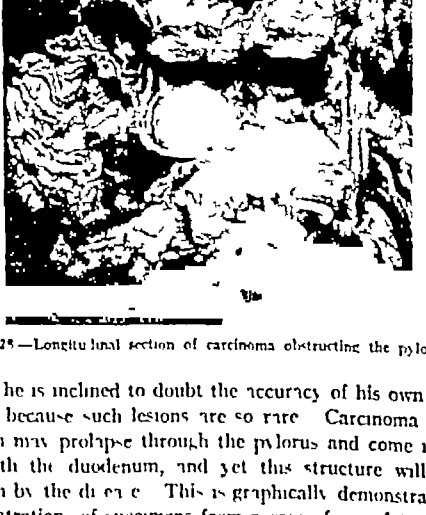

Fig 28—Longitudinal section of carcinoma obstructing the pylorus

denum, he is inclined to doubt the accuracy of his own observations because such lesions are so rare Carcinoma of the stomach may prolapse through the pylorus and come in contact with the duodenum, and yet this structure will resist invasion by the disease This is graphically demonstrated by the illustrations of specimens from a case of complete pyloric obstruction from carcinoma of the stomach (Figs 28, 29)

Nevertheless carcinoma can invade the duodenum During the later years of life carcinoma occurs in all divisions

of the small bowel The history is comparatively short, and the symptoms may be referable to the bowel Abdominal pains or gastric distress may be mistakenly attributed to ulcer or to disease of the gallbladder Indications of intestinal obstruction, either present at the onset of symptoms or developing as the disease progresses, should impel the clinician to absolve the bowel from suspicion by asking for roentgenologic examination Particularly should his attention be directed to the small bowel if the pain tends to have a para-umbilical or

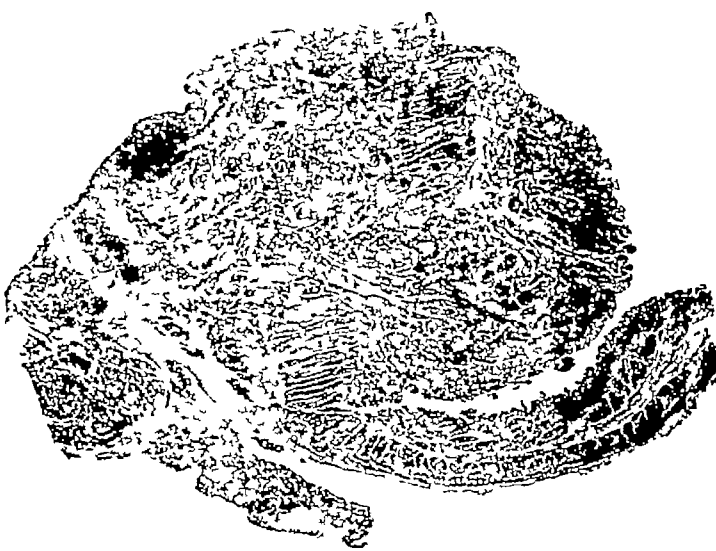

Fig 29 —Microscopic section of the carcinoma shown in Fig 28 The duodenum is not involved

lower abdominal situation Occult or gross hemorrhage may occur Anemia and the persistent appearance of occult blood in the stool must be explained on the basis of a gastro-intestinal lesion which could be in the small bowel, at least the latter possibility should be excluded by roentgenologic examination if the lesions cannot be found elsewhere The roentgenologist finds little evidence upon which to base a diagnosis, and the manifestations are usually limited to signs of obstruction with dilatation and prominent valvulæ conniventes, or, occasion-

ally, a filling defect momentarily observed as the opaque bolus passes along the twenty two feet of small bowel, and the roentgenologist cannot distinguish the type of tumor at all Metastasis is common, and it may be extensive if the lesion is growing rapidly, for early diagnosis of a malignant lesion of the small bowel is seldom made

Case I—A business man sixty five years old had had attacks of abdominal pain for two years At first the attacks had lasted for ten days and had

Fig 30—Small intestine obstructed by carcinoma

recurred at intervals of three weeks but they then had become continuous for the last three months The pain had been colicky had come one and a half hours after taking food and had been associated with peristaltic unrest and borborygmi He had lost 90 pounds (40.8 kg.) in a year There had been no constipation and during the last ten days no pain On physical examination the abdomen was found to be distended pulsation of which caused gurgling and borborygmi No masses were felt All laboratory tests including roentgenologic examination of the stomach and colon gave negative results but a roentgenologic examination for retained bowel marked obstruction and distention of the small bowel (Fig 30

At operation a ring carcinoma of the jejunum causing almost complete obstruction was found Excision was made between the distended

bowel and the collapsed bowel A small piece of lymph node attached to the intestinal wall was found to be carcinomatous There was metastasis to the regional nodes and to the liver The patient died four and a half years later

Sarcoma occurs less frequently than carcinoma The files of The Mayo Clinic show twenty-seven cases to date, including the present nine cases The clinical history and physical and roentgenologic signs differ little from those of carcinoma, and the differential diagnosis must be made by microscopic examination of tissue In this small series, the growth was in the jejunum in four cases, in the duodenum in one case, in the ileum in three cases, and in one case in a segment not specified

BENIGN NEOPLASMS

In 1933, Rankin reported a total of thirty-five cases of benign neoplasm of the small intestine observed at the clinic, since then nine additional cases have been encountered These forty-four cases represent all the benign neoplasms of the small bowel, and the ninety-seven, all the malignant neoplasms, a total of 141 neoplastic growths in this part as compared to thousands occurring elsewhere in the body This difference in the localization of neoplasms is interesting and invites careful study Benign neoplasms occur in the earlier, mature years of life About half of the tumors were discovered accidentally, and only half of them produced symptoms referable to a lesion When symptoms were present, they had existed for a number of years before receiving serious attention Usually the tumor was found unexpectedly at operation, but it was occasionally possible to make the diagnosis by roentgenologic examination The symptoms, when present, often resembled those of ulcer Hematemesis and melena sometimes occurred and, in a few cases, were prominent symptoms Sometimes the distress was regarded clinically as probably due to disease of the gallbladder In a few cases an elusive tumor was palpable About half of the patients with symptoms from the tumor had signs and symptoms of obstruction Of these there were two classes In one class there was a sudden, sharp, colicky pain, with abdominal distention, nausea and

vomiting, in the other, there were slowly increasing signs of distention, borborygmi and pain, perhaps with visible peristalsis The acute symptoms of obstruction are caused by intussusception, and the more slowly developing signs of obstruction are due to gradual encroachment of the tumor on the lumen of the bowel Intussusception in the earlier years of mature life can be suspected as being associated with benign tumor When the diagnosis of a benign or malignant neo-

TABLE 1

INTRINSIC LESIONS OF THE SMALL INTESTINE 1929 TO 1933 INCLUSIVE SURGICAL AND NONSURGICAL CASES

Neoplasms	Duodenum	Jejunum	Ileum	Unspecified	Total
Malignant	4	13	10	4	31
Carcinoma	3	9	7	3	22
Sarcoma	1	4	3	1	9
Benign	7	3	10	1	21
Myoma	3	1	3		7
Polyp	3		3		6
Hemangioma			2	1	3
Lipoma		1	1		2
Adenoma	1				1
Fibroma		1			1
Cystic tumor			1		1
Total	11	16	20	5	52

plasm of the small bowel is made preoperatively, it must be made on roentgenologic evidence if it is made at all

Myomas.—These were of various types and were the most common benign neoplasms found, of these, three were in the duodenum, one in the jejunum, and three in the ileum The histologic classification of other benign neoplasms and their distribution along the small bowel is shown in Table 1 The clinical history of these lesions furnishes no clue to their situation or nature

Case II—A woman, thirty-two years old, complained of fullness and much gas in the stomach promptly after slight meals She had had a definite, specific pelvic infection and, except for one induced abortion, never had been pregnant There had been no abdominal pain or constipation Two months prior to registration she had felt a tumor low in her abdomen On examination, this tumor proved to be mobile enough to be shifted from the upper to the lower portion of the abdomen It was not connected with the pelvic organs. At operation, a fibroma was found at the ileojejunal junction extending from the intestinal wall to the root of the mesentery A portion of the intestine with the tumor was resected The tumor proved to be a pure fibromyoma measuring 10 by 8 cm and weighed 470 gm This tumor grew away from the lumen of the bowel and, as it had not caused any symptoms, was not discovered until felt by the patient

Case III—In this case, that of a woman sixty-five years of age, a myxofibroma caused complete blocking of the terminal portion of the ileum for five days It had grown toward the lumen of the bowel and had produced symptoms of obstruction The lesion was removed with 10 inches (25 4 cm) of the ileum

Case IV—More unusual is the benign neoplasm to be described A woman, sixty-two years of age, complained for eighteen years of "indigestion" and sour belching She had had dull epigastric distress occurring irregularly after meals accentuated after large meals Alkalies or crackers had given ease Physical examination gave negative results except for the palpation of a mass in the right upper abdominal quadrant which was believed to be the gallbladder Laboratory studies including roentgenologic examination of the gallbladder also gave negative results, but roentgenologic examination of the stomach revealed a pedunculated polyp, 1 5 cm in diameter, on the greater curvature of the first portion of the duodenum An exploratory operation of the abdomen including the gallbladder disclosed nothing of significance except a polyp on the anterior wall of the duodenum measuring about 1.5 cm by 1 cm by 8 mm, it was removed and on microscopic examination proved to be an accessory pedunculated pancreas As this polyp consisted of pancreatic tissue, malignant change, such as that to which most polyps of the digestive tract are subject would not be expected to occur

MISCELLANEOUS LESIONS OF THE SMALL BOWEL

Under this heading were classed 414 cases, many of them bizarre and some of them of less interest than others because the lesions were congenital anomalies (Table 2) In other cases the lesions invited study and consideration because of their frequency or because of the nature of the disease process

Diverticula—Meckel's diverticulum was found in ninety-seven cases in the five years, and other forms of diverticulum, in eighty-four cases As one would expect, the second most

frequent location of an acquired diverticulum was the duodenum, in seventy-one cases, there was a duodenal diverticulum, in ten cases the diverticulum was in the jejunum, and in three, in the ileum

TABLE 2

INTRINSIC LESIONS OF THE SMALL INTESTINE 1929 TO 1933 INCLUSIVE SURGICAL AND NONSURGICAL CASES

Miscellaneous lesions	Duodenum	Jejunum	Ileum	Unspecified	Total
Meckel's diverticulum			97		97
Diverticulum other types	71	10	3		84
Fistula	11	6	58	2	77
Intrinsic obstruction due to ileus 28 volvulus 16 or intussusception 8	1	1	15	35	52
Inflammation (mass formation 11)	1	7	18	6	32
Tuberculosis		1	23	8	32
Enlargement (dilatation or stasis)	9	4	1	2	16
Ulcer			6	1	7
Anomalous (congenital)	2		1	4	7
Constriction or kink (idiopathic)		1	2		3
Accessory pancreas	3				3
Para duodenal hernia	2				2
Deformity (due to spasm)	1			1	
Total	101	30	4	59	414

Fraser left little unsaid regarding diverticula of the jejunum and ileum and his comments were equally pertinent to those of the duodenum He has proposed an interesting classification of diverticula as follows (1) congenital diverticula enterogenous and Meckel's diverticula By enterogenous I meant those diverticula that result from the development of embryonic aberrated nest of cells which develop into cysts

that may be attached to any part of the intestine and, after entering the lumen, produce diverticula Meckel's diverticula are subject to many modifications depending on the nature of the active pathologic process (2) Acquired diverticula anomalous and false diverticula Anomalous diverticula result from tugging by attached tumors or from adhesions, or from softening of caseous nodes False diverticula apparently result from extrusion of the mucosal lining of the bowel through a weakened spot in the muscle fibers, usually at the site of entrance of a blood vessel Fraser contended that they start at the mesenteric side of the bowel, but other types of diverticula may also occur at undesignated places He found two cases of false diverticula of the small bowel among 5,000 cases at the Royal Victoria Hospital, Belfast Such diverticula are usually multiple and, although common in the large bowel, are comparatively rare in the small bowel From a practical clinical point of view the classification has little value, for, theoretically, all diverticula are capable of producing complications, only some are more likely to do so than others

Diverticula of the small bowel tend to be larger than those of the large bowel and, as a rule, have large gaping orifices, whereas diverticula of the large bowel are likely to have a narrow neck, favoring retention of fecal material that leads to infection (diverticulitis) and its symptoms of a painful, tender spot, with systemic symptoms of toxemia and, perhaps, with chills and fever As the inflammatory process advances, a palpable mass appears, and with its enlargement, there is encroachment upon the lumen of the bowel with increasing signs of obstruction Such a process occasionally results from diverticulitis It is so rare in the small bowel in our experience that it has never been diagnosed I could find no proved instance of inflammation of an acquired diverticulum of the small bowel in this series reported from the clinic Diverticulitis of the small bowel is a disease without much clinical interest, perhaps the diagnosis is being overlooked The following two case reports illustrate what might be taken for symptoms from diverticula in the small bowel

Case I.—A dentist forty nine years of age slight in stature and of nervous temperament from youth a victim of migraine from boyhood and of many nervous breakdowns," had had attacks of vague gastric distress and pyrosis which had been relieved by following a low carbohydrate diet for alimentary glycosuria. Two years before his admission he had begun to have real epigastric pain which had occurred at 11 a. m. and had progressed in spite of meals until evening when he had usually obtained relief. If not, vomiting had sometimes given partial relief. Because of this atypical history of ulcer a complete roentgenologic study of the digestive tract was made. The gallbladder was found to function normally. The stomach and duodenal bulb were normal. There were however multiple diverticula in the small bowel extending from

FIG. 31.—Multiple diverticula of the small intestine.

Case VI—An attorney was forty-six years of age, when he first came to the clinic Since the age of eight he had had epigastric distress twenty minutes after meals, with a sudden nausea and vomiting and then relief, when under mental strain For twenty-seven years he had had chronic malaria When first seen, chronic malaria and gastritis nervosa had been diagnosed after complete study Five years later he had had an attack of acute right upper abdominal pain with residual soreness for two weeks, and thereafter, for four months, he had had frequent transitory pain at the right costal margin and a fullness occurring even at night This had required alkalies for relief The total gastric acidity (Topfer's method) was 102, free hydrochloric acid 92, and roentgenologic examination of the stomach and duodenum disclosed a large diverticulum in the second portion of the duodenum Cholecystography indicated that the gallbladder was functioning normally, yet it was thought that there was cholecystic disease and that the diverticulum was of little importance

Fig 32—Diverticulum of duodenum

Operation, in April of 1932, revealed only the diverticulum in the second portion of the duodenum This diverticulum was about 4 cm in diameter, and its walls were flaccid The base of the diverticulum was over the head of the pancreas Rather than dissect it, it was suspended into the lesser peritoneal cavity on the inner surface of the mesocolon The appendix was removed, the gallbladder was found to be normal, and there was an area of thickening on the anterior aspect of the duodenum, at the level of the common duct, which was thought to be due to trauma rather than to ulceration For nine months after the operation the patient was absolutely free from symptoms then epigastric soreness developed It gradually got worse until it became a constant severe pain, and his discomfort was augmented by cutting pains in the right umbilical region He resorted to sedatives After six days of study in the hospital, during which time he was found to have total gastric acidity of 84 and free hydrochloric acid of 66 and another roentgenologic examina-

tion disclosed only a large diverticulum in the second portion of the duodenum he was dismissed to follow an ulcer regimen Eight months later he said in a letter that he was preparing to be operated on for duodenal ulcer

Both of these cases might be considered instances of symptoms from diverticulitis of the small bowel which were overlooked (Fig 32)

Fistula.—After diverticula, the next most common lesion of the small bowel in this five-year group, including neoplasms was fistula most all were postoperative They do not represent intrinsic lesions of the small bowel, but they were not discarded from consideration, as adhesions were, because the small bowel was so completely involved by the lesion There were seventy seven of these cases The ileum was most frequently involved in fifty-eight cases, the duodenum was involved in eleven and the jejunum in six The fistulas not specifically located in two cases belonged probably to either the jejunum or ileum Eight were not the result of previous operation One was caused by perforation of the small intestine one by rupture of empyema of the gallbladder, two by pelvic abscess, two by tuberculosis of the bowel, and two by gunshot wounds The operations that were followed by fistulas were, in order of frequency operation on the appendix, forty-one operation on the gallbladder, five, pelvic operation resection of the large bowel for carcinoma, and operation for intestinal obstruction of obscure nature, four each operation on the stomach three abdominal exploration splenectomy and operation on the kidney two each, and operation for inguinal hernia and diaphragmatic hernia one each

INTRINSIC OBSTRUCTION OF THE SMALL BOWEL (ILEUS VOLVULUS INTUSSUSCEPTION)

Intrinsic occlusion of the lumen of the small bowel occurred in fifty two cases By ileus is meant colicky pain arising from a segment of the bowel due to local failure of peristaltic function but from a cause not determined Dilatation of the bowel is usually extreme and the patient's condition critical so that detailed exploration is not possible Only once was the

lesion causing ileus accurately located, and then, oddly enough, in the duodenum In the other twenty-seven cases in which ileus was diagnosed, the paralyzed segment was not found, but it was either in the ileum or jejunum Volvulus occurred in sixteen cases, in the jejunum in one, in the ileum in nine, and in six the affected segment was not noted In all cases in which the cause was determined, it proved to be adhesions Twice the lesion occurred in conjunction with acute appendicitis, and in the remainder, followed immediately after operation or as a delayed complication In two cases in the series, the cause of volvulus was not discovered Intussusception occurred in eight cases When the segment involved in the intussusception was determined, it was found always to be in the ileum In all of these cases, the patients were children from four months to fifteen years of age, although the condition can occur in the mature years of life In two of the eight cases, the segment was not identified In these children the intussusception followed appendectomy in two cases, in the others, it occurred spontaneously Symptomatically, these lesions are suspected clinically only by signs of obstruction of the small bowel, namely, cramp-like pains low in the abdomen, sudden in onset and often para-umbilical in situation Cramps from obstruction of the small bowel recur at shorter intervals than those from obstruction of the large bowel Other than these features, the symptoms of obstruction of the small bowel resulting from ileus, volvulus, or intussusception are the same as those produced by other varieties of obstruction

Inflammation —The majority of the thirty-two cases of inflammation of the small bowel presented symptoms of obstruction of the bowel On the other hand diarrhea was a frequent symptom and, occasionally, there was pain and tenderness Diagnosis, of course, was made from the roentgenologic signs of obstruction and the effacement of the mucosal folds of the small bowel that bespeak inflammation At operation, the inflamed segment sometimes appeared as a mass resembling that produced by tuberculosis or malignant disease, but microscopic examination of the removed tissue revealed non-

specific inflammation, occasionally with marked edema and giant cells Edema of the tissues was often apparent grossly The distributions of these lesions along the small bowel was as follows in the duodenum, one (except duodenitis), in the jejunum, seven, in the ileum, eighteen and six unspecified

Tuberculosis —The thirty-two cases of tuberculosis of the small bowel were classical as to symptoms Usually, the intestinal lesion was associated with tuberculosis elsewhere, often with pulmonary tuberculosis This series confirmed the fact that tuberculosis of the bowel usually is confined to the terminal part of the ileum and proximal part of the colon In one case the tuberculous lesion was in the jejunum at the duodenojejunal junction and associated with a mass of caseous nodes In this case the disease may not have started in the jejunum at all The symptoms of tuberculosis of the small bowel were at first a vague dyspepsia but, as the disease became more advanced, pain and diarrhea followed, perhaps alternating with constipation Nausea brought loss of appetite and consequent rapid loss of weight In the hyperplastic type, with its fibrous hyperplasia, thickening and rigidity of the intestinal wall and narrowing of the lumen, constipation resulted Palpation of the abdomen commonly revealed doughy resistance, as in any form of chronic peritonitis Roentgenograms aid in the diagnosis by disclosing a filling defect, obstruction of the bowel or hyperperistalsis The demonstration of bacilli of tuberculosis in the stool is of questionable value, for it has been shown that they are often present in the stool as a result of pulmonary tuberculosis alone

mation disclosed ulcerative tuberculosis in the ileocecal area and ascending colon At operation, the distal portions of the ileum, cecum and ascending colon were resected for tuberculosis and multiple ulcers, and regional tuberculous lymph nodes also were removed

Ulcers of the Ileum—There were seven cases of simple, nonspecific ulcer of the small bowel Operation was performed in four cases because of unexplained melena which in three cases was associated with chronic anemia, and in one, with cramp-like abdominal pain Three patients were operated on because of obstruction, two of them had frank and complete obstruction of the bowel, and one, cramp-like pains, distention, and diarrhea characteristic of incomplete obstruction In two cases, at operation, a Meckel's diverticulum was found, but the ulceration was separate and distinct In three cases the ulcers were annular In one case there were multiple longitudinal ulcers and in one, a perforating ulcer associated with bands causing obstruction

Simple ulcers of the small bowel are rare When they occur, however, they produce bleeding or obstruction and, sometimes, pain and diarrhea

Case VIII—A man, forty-seven years of age, came to the clinic because of weakness, dyspepsia and cardiac palpitation This palpitation had been present for seven years but had become worse during the preceding seven months He had previously received treatment for cardiac disease Eight years before admission, he had had melena and this had recurred about every six months The last tarry stool had been noted three months previously He had become weakest at the time melena had occurred There were no symptoms of disease of the stomach or gallbladder On physical examination the patient appeared to be poorly developed, thin, and pale He had a diffuse adenomatous enlargement of the thyroid gland, 2.5 by 4 cm The heart was not enlarged, but there was an apical systolic murmur that was transmitted to the axilla The systolic blood pressure was 142 and the diastolic 70, the pulse rate was 102 beats per minute and the temperature 99.2° F There was no edema

The patient's basal metabolic rate was elevated to + 19 per cent Repeated studies of the blood, including the blood count, bleeding time, coagulation time, clot retraction, prothrombin time, volume, and morphologic characteristics, led to no specific diagnosis other than secondary anemia The lowest readings were hemoglobin 30 per cent (Dare), erythrocytes 2,740 000 per cubic millimeter, index 5 plus, and leukocytes 4,200 per cubic millimeter The differential count was normal Morphologic study of the cells disclosed marked hypochromasia, and good regeneration of the cells The urine was normal Roent-

genologic examinations of the thorax stomach and colon gave negative result Roentgenologic examination of the small bowel was not made Other laboratory studies and special examinations gave negative results they included examination of the stools for blood and proctoscopic examination that revealed nothing more than hemorrhoids

After transfusion partial thyroidectomy was performed for multiple adenomas of the left lobe Subsequently the abdomen was explored for possible bleeding points blood dyscrasia having been excluded The spleen was found to be enlarged grade 4 and the liver stomach and duodenum were normal In the ileum was a stricture of inflammatory nature with 5 inches (12 7 cm) of distended bowel above having strictures on its walls this indicated that the dilatation was of long standing Ten centimeters of the ileum was resected and end to-end anastomosis of the bowel was made On examination of the resected portion the pathologist found an inflammatory annular ulcer 6 mm in diameter containing lymphoid tissue

Odd Cases—The congenital anomalies do not require discussion they were museum records and for simplicity of study might have been omitted, but, as it was attempted in this study to be thorough and include all intrinsic lesions of the small bowel seen during the period, they were left in the tables for contemplation by the curious

SUMMARY

A pathologic and anatomic classification of the various intrinsic lesions of the small bowel, occurring in a five year period, is given, in which are cited the cardinal symptoms of each group No attempt is made to explain the paucity of lesions in the small bowel When the small bowel was markedly involved from extrinsic causes as in cases of fistula such lesions also were considered Because lesions of the small bowel are scarce, study of a larger series of patients might change the incidence given, or else add to the isolated congenital anomalies that were merely mentioned in the tables and not discussed

Unexplained abdominal pain with or without gross or occult bleeding or anemia, calls for investigation of the small bowel The most commonly recognized sign of disease in the small bowel is obstruction With present knowledge preoperative study is inadequate for accurate diagnosis In serious cases diagnostic exploration is justifiable

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THE PRESENT STATUS OF THE DIAGNOSIS AND TREATMENT OF ADDISON'S DISEASE

ALBERT M SNELL

There are few rare disorders which have attracted as much attention as Addison s disease Because of the striking nature of the condition and because of the fact that our knowledge of it is so intimately connected with the study of the physiology of the suprarenal gland, the disease has been studied with great thoroughness by physiologists, pathologists, and clinicians since the time of Addison's original description These labors unfortunately have been largely unrewarded until recently With the isolation of the cortical hormone and the demonstration of the relation of this substance to the metabolism of salt a new impetus has been given to study of the disease The advances in diagnosis and methods of treatment, which have been made in the last few years, are sufficiently promising to warrant an optimistic view for the future, and it is perhaps not too much to hope that this hitherto fatal condition may be brought under medical control much as diabetes has been brought under control since the discovery of insulin

Before proceeding to a discussion of Addison s disease, it is important to consider briefly its pathologic physiology The affected structure the suprarenal gland consists of two phylogenetically distinct structures, the cortex, which is derived from the wolffian bodies and the medulla, which arises from the embryonic sympathetic nervous system The suprarenal cortex has long been known to be essential to life, and it is the source of a general cellular hormone, which has possible specific effects on the kidney as shown by its regulatory effects on concentration of blood metabolism of sodium and excretion of nitrogenous waste material The function of the

suprarenal medulla, which is related in structure to the chromaffin system, are not fully understood On the basis of observations after its extirpation, it has been supposed to be a nonessential portion of the suprarenal gland However, there is so much chromaffin tissue, with presumably similar functions, within the organism, that this point cannot be regarded as proved Some evidence exists which seems to indicate that the suprarenal medulla is connected in some way with the formation of pigment, carbohydrate metabolism, and circulatory efficiency In addition, it is the source of epinephrine

About 80 per cent of cases of Addison's disease are associated with fibrocaseous tuberculosis of the suprarenal glands The tuberculous process appears to begin in the medulla and to extend peripherally, thus cutting off fragments of the suprarenal cortex, which may be preserved to form the so-called cortical adenomas These may, in the aggregate, amount to about 10 per cent of the weight of a single suprarenal gland and are probably capable of some functional activity In about 20 per cent of cases, atrophy of the suprarenal gland is responsible for the disease This process, the etiology of which is entirely unknown, begins in the cortex, which appears to collapse on the medulla, occasionally leaving portions of the medullary tissue intact Ordinarily, the entire structure is destroyed, and in fact, a careful search may be required to reveal any suprarenal tissue at necropsy In rare instances, the clinical picture of Addison's disease has been described in such lesions of the suprarenal glands as carcinoma, gumma, hemorrhage, infarction, or chronic inflammatory changes with fibrosis There is a record of one case which followed mycosis fungoides For all practical purposes, however, tuberculosis and atrophy are the only lesions of the suprarenal gland which need to be considered

INCIDENCE

About 300 to 400 cases of Addison's disease are reported annually in the registration area of the United States, the death rate is remarkably constant, being about 0 4 per 100,000 of the population At The Mayo Clinic, about 155 cases have

been encountered in the last twenty two years It is a disease of middle life, occurring most commonly in the fourth or fifth decade, cases have been described among children, the youngest patient observed here was thirteen years of age Males are affected about twice as often as females There is no evidence to indicate that the incidence of the disease is increasing, the larger number of cases reported is largely a matter of increased diagnostic acumen

DIAGNOSIS

It is difficult to give the essential facts of diagnosis in any better fashion than that employed by Addison in his original description "The leading and characteristic features of the morbid state to which I would direct attention are anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change in the color of the skin" It is now known that the disease presents two characteristic sets of symptoms and signs those of the stage of chronicity and those of crisis The principal symptoms of the former are slight asthenia, hypotension, pigmentation of the skin (Fig 33), and occasionally phenomena related to hypoglycemia These may persist for long periods before the more serious nature of the disease becomes apparent It has been suggested that these symptoms are results of dysfunction of the medullary portion of the gland and that they are associated in some way with disturbances in the normal formation of epinephrine Bloch and others have advanced theories attributing the pigmentation to a breaking down of the precursors of epinephrine in the skin The theoretical relation of failure to formation of epinephrine to such symptoms as weakness hypotension and hypoglycemia is, of course obvious It is interesting to note that the symptoms of chronicity have not been satisfactorily produced in the experimental animal and that in the patient they are not entirely amenable to treatment with cortical hormone

The more serious symptoms of the disease are those of crisis which are intimately related to the destruction of the

cortex of the gland and to loss of the cortical hormone These may develop at any time in latent cases or may develop *per passu* with the pigmentation and asthenia Often they appear without warning, but more frequently the initial symptoms develop gradually These symptoms, which have been described under the heading of "suprarenal insufficiency," are entirely comparable to those seen in the bilaterally adrenal ectomized animal Anorexia, nausea, vomiting, diarrhea, and

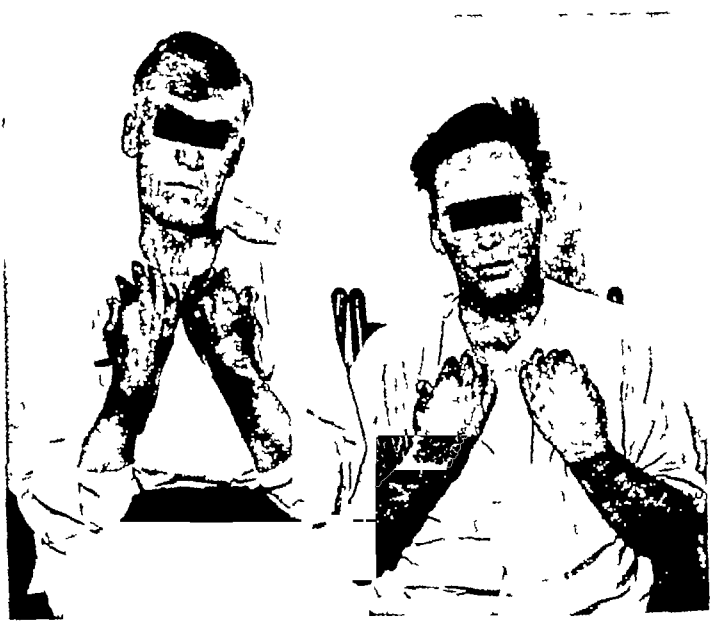

Fig 33 —Appearance of 2 patients who had Addison's disease The pigmentation on exposed surfaces is evident

circulatory collapse are those which are most commonly encountered, and the development of these symptoms is attended by fairly characteristic changes in the bodily chemistry These episodes of so-called crisis are attended by loss of sodium from the body (Harrop and his collaborators[6]), with equivalent loss of chloride and bicarbonate ions and their probable complement of body water The loss of fluid and salt which results from vomiting and diarrhea is incidental, and is not sufficiently great to account for the changes which are observed

It has been shown that excretion of sodium takes place chiefly by way of the kidneys and results eventually in marked loss of water and concentration of blood There is usually an associated accumulation of nitrogenous waste in the blood, the blood urea, nonprotein nitrogen, and serum sulphates rising rapidly The serum potassium is also increased, often out of proportion to the degree of concentration of the blood The total base and the carbon dioxide combining power of the blood are reduced, chiefly because of the loss of sodium ions These findings, which were first emphasized by Loeb,[11] and later by Harrop and his collaborators,[7] are of great significance, and a thorough appreciation of their importance is essential to adequate treatment, since the symptoms of suprarenal cortical insufficiency both in patients and in experimental animals, may be relieved in a striking manner by the administration of the cortical hormone and by the restoration of fluids and sodium salts

It is apparent from the preceding that it is necessary to distinguish clearly between the stage of latency and the stage of crisis in Addison's disease in order to advise logical treatment The diagnosis of the disease especially during periods of latency, depends almost entirely on the demonstration of pigmentation of the skin, since hypotension, loss of weight, and vague digestive disturbances are commonly encountered in a number of other disorders While the pigmentation varies greatly in different cases there are certain characteristics which are almost diagnostic The color of the skin is most frequently a dirty grayish brown the discoloration being most pronounced on the exposed surfaces of the body The pigmentation is diffuse, but pressure points scars, and bony prominences are definitely darker than the surrounding areas of skin Minute black freckles are often noted, especially on the neck and shoulders The genitalia, anus, axillæ, nipples, and lips may be strikingly discolored even with absence of conspicuous general pigmentation On the oral mucous membranes especially the buccal surface, tongue, and gums are brownish or purplish patches, which are very typical The

hands often have a negroid appearance, the palm is distinctly lighter than the dorsum, and a well-marked line of demarcation is noticeable, the lines of the palms may stand out because of the deposits of pigment in these areas Such pigmentation, occurring as it most frequently does in an asthenic individual, can hardly be mistaken for that of any other disease The pigmentation may occasionally be confused with that of hemochromatosis, acanthosis nigricans, arsenical poisoning, and vagabond's disease Biopsy of the skin, with the employment of appropriate stains for iron and arsenic, usually will serve to distinguish these other conditions, since in these disorders the skin presents a more or less characteristic microscopic appearance, while in Addison's disease it is essentially normal, except for the increased quantities of melanin Biopsy is, therefore, largely of negative value in diagnosis

The demonstration of tuberculosis elsewhere in the body is of considerable importance both from the standpoint of diagnosis and of treatment About one patient in three will have demonstrable tuberculosis of the lungs, lymph nodes, bones, or genito-urinary tract The association of pigmentation of the skin with demonstrable tuberculous lesions anywhere in the body, or even with conclusive evidence of a previous tuberculous lesion, is of considerable significance in diagnosis The demonstration of calcification in the suprarenal gland itself, which is almost *prima facie* evidence of tuberculous involvement, is also of great importance Using the roentgenologic technic, which has been developed by Camp and his associates, it is possible to demonstrate calcification in approximately 25 per cent of cases of Addison's disease In our experience, the presence of definite suprarenal calcification is, for all practical purposes, pathognomonic of Addison's disease

It should not be inferred from the preceding that all cases of the disease present a typical picture or one which is easily recognized There are many cases in which the pigmentation of the skin is slight or atypical, and in which it is impossible to demonstrate calcification of the suprarenal glands, or evidence of tuberculosis elsewhere in the body Diagnosis

in such cases is at best difficult particularly if neurocirculatory asthenia and vague digestive disturbances also are present It may be facilitated by the procedure which Harrop first suggested, that of deprivation of salt. As previously mentioned, the principal feature of acute suprarenal insufficiency is loss of sodium from the body this loss apparently is intimately connected with deficiency in production of the cortical hormone By withdrawing salt from the diet of patients who have latent Addison's disease it usually is possible to produce symptoms of crisis and characteristic changes in the chlorides and nitrogenous components of the blood In cases in which the individuals are normal and have intact suprarenal glands, deprivation of salt produces no clinical symptoms and only minor changes in blood chemistry, whereas, in Addison's disease, striking changes in the general condition of the patient and in the blood chemistry are usually obtained This procedure has been employed at the clinic in a number of instances and, while not without its dangers, it may be of great importance in diagnosis in the doubtful case Reiman has told me of one instance in which deprivation of salt failed to produce crisis in a case of Addison's disease although the patient expired with typical symptoms of suprarenal insufficiency within a short time afterward At necropsy, complete destruction of both suprarenal glands was found This appears to be the exception and not the rule however and it is believed that the procedure should give reliable information in a large majority of cases This provocative test should never be employed unless the patient is under close observation in a hospital with every facility for emergency treatment at hand dangerous collapse may be precipitated in this fashion and extraordinary measures may be required to avoid a fatal termination

One is often asked if the diagnosis of the disease can be made in the absence of pigmentation, or if it can be established with certainty in cases in which the skin of the patient normally is dark Diagnosis in the absence of pigmentation is of course a difficult matter Fortunately such cases are decidedly infrequent although a number of them have been

reported in the literature, chiefly after necropsy I know of one case in which Rowntree[4] made the correct diagnosis in a case in which there was no pigmentation Usually, a positive diagnosis of Addison's disease cannot be made with certainty in the absence of typical pigmentation unless one can demonstrate calcification in a suprarenal gland or provoke the clinical and chemical phenomena of crisis by withdrawing salt from the patient's diet

There is one other feature of diagnosis which deserves particular attention, and this has to do with early recognition of the signs of suprarenal insufficiency Anorexia, nausea, vomiting, and increasing asthenia are among the earlier phenomena associated with this condition, and patients who present such symptoms may pass into a state of shock within a few hours Marked nervous disturbances, such as restlessness, delirium, coma, and meningismus may be noted There is often marked hyperthermia during such episodes These crises are precipitated by exposure, exertion, catharsis, surgical procedures, or any condition which makes unusual demands on the affected individual Fortunately, the early stages of crisis are usually attended by a fall in the concentration of blood chlorides, a rise in the urea nitrogen of the blood, and the other chemical phenomena of crisis which have been mentioned previously It therefore becomes imperative to be on the lookout for these signs and symptoms and to make prompt examination of the blood in cases in which suprarenal insufficiency is suspected I know of a number of instances in which such patients were admitted to the hospital as emergency cases, and the true state of affairs was not discovered until too late to institute appropriate treatment

TREATMENT

There are, of course, two obvious indications in the treatment of Addison's disease The first is to maintain an adequate supply of sodium salts, and fluids, the second is to supply the missing cortical hormone The relative importance of these two factors has been much debated in recent years Many workers have felt that the cortical hormone was rela-

tively unimportant and that the use of physiologic saline solution alone produces therapeutic results which are approximately as good as those obtained by giving physiologic saline solution and the hormone conjointly Rogoff and Stewart pointed out long ago that the intravenous administration of physiologic saline solution would considerably prolong the life of the bilaterally adrenalectomized animal Zwemer has recently demonstrated that the use of calculated amounts of sodium salts, particularly the bicarbonate and the chloride, prolonged the survival period of adrenalectomized cats to an average of about eighteen and four tenths days, whereas, the best control subjects did not survive more than ten days The administration of salt solutions intravenously, or even of salt by mouth, to patients, has produced comparable results Loeb[10, 13, 14] has emphasized this point, and in retrospect it is easy to see how some of our earlier addisonian patients were salvaged from episodes of suprarenal insufficiency by the use of physiologic saline solution alone I have encountered a few patients who had latent Addison's disease and who had marked and abnormal craving for salt One patient used it literally by the handful, and is still in remarkably good condition, although his skin has been definitely and typically pigmented for more than five years Another patient was in the habit of emptying the entire contents of the saltcellar on his food at each meal, he also has remained in a stage of latency for an unusually long period The importance of an adequate intake of sodium salts in the treatment of Addison's disease can hardly be overestimated the daily basic requirements are from 6 to 12 gm it can be administered in gelatin capsules or enteric pills or even by using physiologic saline solution as a beverage* A high salt intake is essential in the latent or

* Recent studies indicate that sodium salts other than chloride are necessary to maintain suprarenalectomized animals in optimal condition. Two groups of investigators (Allen W D The influence of diet and mineral metabolism on dogs after suprarenalectomy Proc Staff Meetings Mayo Clinic 10 406–409 (June 1) 1935 and Harrop G A Soffer L J Jr Nabrelson W M and Strauss Margaret Studies on the suprarenal cortex IV The effect of sodium salts in sustaining the suprarenalectomized d Jour Exper Med,

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chronic case and, of course, in the treatment of a patient who presents symptoms of crisis It has been noted that patients who are receiving maintenance doses of cortical hormone will have mild symptoms of collapse when salt is withdrawn, and it has been also observed that the hormone appears to act in a much more effective manner if an adequate intake of salt is maintained A similar situation prevails in the experimental animal

The reputation of the cortical hormone has suffered somewhat because of the fact that the available commercial preparations have varied considerably in potency, and in some instances have been completely inert Certain commercial lots have been ineffective in maintaining life of the experimental animal, as Rogoff[16] has demonstrated, but the fault obviously lies not with the hormone itself but with the method of its preparation As many investigators have demonstrated the free administration of the hormone to adrenalectomized animals will prolong life indefinitely Swingle, Pfiffner, Vars and Parkins[23, 24] later demonstrated that the blood of the adrenalectomized dog is diluted after injection of the hormone, even if the dog is deprived of fluids and salt They found, however, that the blood pressure, the hemoglobin, and the urea of the blood did not return to normal unless fluids and salt were administered It has been demonstrated that patients, who have severe suprarenal insufficiency, may undergo marked improvement or recovery even when no special attempt has been made to provide salt or fluids In this connection, one may cite the earlier reports of Rowntree and his collaborators,[18] and the reported case of Cantor and Scott, their patient was revived from periods of crisis fourteen times in twenty-six months by the use of the hormone Rynearson and I recently have

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61 839–860 [June 1], 1935) have shown that suprarenalectomized dogs can be maintained indefinitely by diets containing sodium chloride and sodium bicarbonate in adequate amounts without the addition of any cortical extract Clinical data on this point are lacking, but the addition of the sodium salts of organic acids, in addition to the treatment just mentioned, promises to be a valuable procedure

studied a patient who had Addison's disease, who remained in a state of chronic relapse, and who was extremely sensitive to the withdrawal of either salt or the hormone It was impossible to maintain this patient in good condition even when salt was administered liberally by mouth and by vein, while the electrolytes of the blood remained within normal range, marked anorexia developed, with abdominal pain, profound asthenia, and other signs of impending crisis This individual could be kept in reasonably good condition with large amounts of the hormone and a diet containing about a normal amount of sodium chloride (6 gm), it required both extra salt and adequate amounts of the hormone to maintain the patient in optimal condition As Swingle and his collaborators[23 24] observed in regard to their experimental animals, placing fluid and salt at their disposal was one thing, the retention and utilization of these substances by a subject who has a deficiency of the cortical hormone is something altogether different I have also noted a number of patients who have been maintained in a state of semi invalidism with minimal amounts of hormone and an adequate supply of salt In each of these cases an increased dosage of cortical hormone brought about marked and immediate improvement in the general condition of the patient and an increase in strength and appetite and a gain in weight While difficult to measure, and perhaps unconvincing to those who wish to be skeptical about the effects of the hormone, the improvement is nevertheless genuine and striking It should perhaps be said that at the clinic we have had the advantage of freshly prepared cortical hormone prepared by Kendall's methods and generously supplied by him and that the results are not strictly comparable to those which may be expected from the use of commercially prepared extracts The latter preparations are constantly being improved in potency and may soon be on a par with the best laboratory products

The requirements for treatment in the various stages of Addison's disease are difficult to anticipate and must be highly individualized There are a considerable number of patient

cases in which no hormone whatever is needed and the patients get along comfortably on a normal intake of salt A few of these remarkably long-lived and fortunate patients have been observed at the clinic Unfortunately the compensatory mechanisms that come into play under these circumstances are entirely unknown It can only be assumed that a substantial amount of the suprarenal cortex is present either in the periphery of the diseased gland or elsewhere in the body A few patients in moderately severe condition have been able to get along comfortably by taking extra sodium chloride One patient, who was observed recently, maintained a reasonable state of health for about eight months, but lapsed into severe crisis within forty-eight hours after being deprived of salt She has since begun the use of cortical hormone with remarkable improvement in her general health It is possible that such individuals elaborate a sufficient amount of cortical hormone to meet ordinary requirements if the intake of sodium chloride is maintained at a high level, although their general state of health may be poor Other patients remain in what Harrop has called "chronic relapse," and require large amounts of the hormone and increased intake of salt to maintain life I have noted that a number of our chronic patients have lapsed into such a state, which is perhaps best explained by progressive destruction of suprarenal cortical tissue It is possible that such individuals are the nearest clinical parallels of the completely adrenalectomized animal, and that they are able to maintain life only under ideal conditions The tendency of these individuals to lose sodium is probably great, and in certain cases the free use of intravenously administered sodium chloride is necessary Neither the maintenance of normal salt metabolism nor the administration of large amounts of potent cortical hormone suffice to restore such patients to normal health Are there additional hormones which need to be replaced, or do compensatory mechanisms which operate in some cases fail in others? These questions cannot be answered at the present time, but it is entirely probable that the next great advances in the treatment of

Addison's disease will be along these lines Wilder recently has published some studies on the use of extract of the anterior lobe of the pituitary body in Addison's disease, which is based on the work of Kraus, who demonstrated regressive changes in the chromophile cells of the pituitary body in cases of Addison's disease Wilder's observations indicate that there is some reduction in the sensitiveness to deprivation of sodium chloride in patients who are receiving an extract of the anterior lobe of the pituitary body In one case in which the patient had been maintained in a state of invalidism for several months on large doses of the suprarenal cortical hormone and sodium chloride, the use of this extract of the anterior lobe of the pituitary body produced marked general gain in weight and strength This problem warrants much further study, and it may be that more information about the behavior of other endocrine glands in Addison's disease will lead to marked advances in the effectiveness of therapy

A word in regard to the dosage of cortical hormone is necessary, although entirely satisfactory directions for its use are difficult to outline, since both the potency of the preparation and the requirements of the patient may vary over a wide range To date standardization on the basis of dog units (cubic centimeters of extract required to maintain the bilaterally adrenalectomized dog as expressed per kilogram of body weight) has not been satisfactory, and there is no adequate physiologic yardstick which measures the effect on the patient The amounts of hormone required have been determined largely on a basis of clinical experience, which is in effect a process of trial and error In crisis the requirements are large (10 to 20 c c or more daily) The presence of infection calls for even greater amounts, as has been thoroughly demonstrated in the experimental animal Following syndromes of acute insufficiency it may be necessary to continue with large amounts of hormone for several days before the dose can be reduced with safety Maintenance dosage can be determined only by such gradual reductions in dosage the general condition of the patient being carefully observed A rapid falling

off in caloric intake and body weight is a danger signal, good appetite and a rising weight curve are synonymous with adequate treatment In general, small doses (1 to 5 c c) of the hormone are virtually useless, in most instances the patient needs either 5 c c or more or no hormone at all Subcutaneous administration is possible with most preparations, but the intravenous route is a necessity in an emergency No toxic effects have been noted, the failures are attributable to insufficient hormone rather than to overdosage

RESULTS OF TREATMENT

The statistics on all cases of Addison's disease in which treatment has been administered have been published recently,[21] and need not be referred to in detail Three essential points stand out (1) The morbidity of the disease has been greatly decreased by present methods of treatment (2) There is definite evidence that life is being prolonged beyond the figures established by Guttman (3) Atrophy of the suprarenal gland is more prominent as a cause of death than before, presumably because of the survival of fragments of cortical tissue in tuberculous lesions which, with some assistance in the form of hormone treatment, may suffice to maintain life During the year 1934, not a single patient who had Addison's disease died while in Rochester Two died elsewhere because of circumstances in which it was impossible to meet the requirement of emergency treatment with sufficient promptness More of our patients are living and in good condition than at any time in the last ten years A number of them are actively engaged in earning a livelihood, several of them at rather strenuous occupations In certain of the more severe cases, the patients are obviously restricted in their activities It has been possible to perform successfully a major surgical operation (nephrectomy)[22] in one case in which the patient had severe Addison's disease This may be regarded as a distinct triumph for present methods of treatment, since heretofore almost all surgical operations on patients with Addison's disease terminated fatally (Rowntree and Snell) In general,

it appears that a hopeful attitude with regard to the treatment of the disease is entirely justifiable, since our improved knowledge of the pathologic physiology of suprarenal insufficiency and the rapid improvement which is being made in the preparation of the cortical extracts seem to indicate that the future of patients who have this disease may eventually become as assured as that of those who have diabetes. The isolation of the crystalline hormone by Kendall may well lead to the synthesis of this substance in the near future, with resulting decrease in cost, a better method of unit dosage, and increased efficiency of treatment.

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SEVERE ABDOMINAL PAINS THAT FOLLOW AN EMOTIONAL STORM

WALTER C ALVAREZ AND H CORWIN HINSHAW

Many times a year we see patients who complain of attacks of severe abdominal pain for which an adequate cause has not been found even with repeated examinations and perhaps repeated exploratory laparotomy In some of these cases we learn that the usual or only, cause of the trouble is an emotional upset following some acute annoyance or worry over family or business matters We do not know the mechanism that produces the pain and we cannot give the disease a name, but we see enough of it here at the clinic so that we can be sure now of one thing, and this is that we do not want to advise operation We feel so sure of this that we discourage even the performance of exploratory laparotomy, and we think we can assure the worried patient, from the history alone, that his troubles are functional in origin, and that no matter how long he goes on complaining, severe complications will never develop and he will never die of the disease.

Case 1.—A stout pleasant appearing blond Jewess married and thirty five years of age came to the clinic complaining of having suffered for about a year with attacks of severe pain in the abdomen The fact that this pain centered in the left upper quadrant gave us the first warning that the trouble was probably a so called functional one

The pain usually started under the sternum; it shifted down to the epigastrium then to the left costal margin and then like a knife it extended through to the back under the left shoulder blade Sometimes it doubled her up and at times her physician had to give opiates for relief When she did not get a hypodermic in certain the pain continued for hours There was no nausea or vomiting But the attacks were sometimes preceded by a local well localized pain and there usually was a feeling and presence of flatus Significant was the fact that there was no residual soreness after an attack and between attacks there was practically no discomfort The attacks came at intervals of a few weeks

Repeated examinations in her home city had failed to reveal organic disease, but because she looked like a good candidate for cholecystitis, and because the pain was so severe, the competent physician who saw her in the attacks had wished to remove the gallbladder She hesitated to undergo the operation and sought further advice

When first seen at the clinic, extensive examinations failed to throw any light on the problem She returned home with the advice not to undergo any operations Several months later, when she returned to the clinic because of continuance of the trouble, careful questioning brought out the fact that the paroxysms of pain almost always followed some emotional disturbance attributable to family annoyance or worry, more rarely it was brought on by unusual excitement or fatigue

Doubtless the most enlightening and significant point in this woman's history, as revealing her emotional make-up and the intensity of her reactions, was her statement that she "cried for a month" when her brother lost all his money At first sight, one would not think of her as a decidedly neurotic person because she looked so fat and good natured, but all neurotics are not thin and scrawny, as we learned recently when a young woman, weighing more than 250 pounds (117 1 kg) put on the best show of major hysteria that we have seen for many a year

But to get back to the patient in the case reported, she was exhorted to put on the brakes as soon as she felt herself slipping into a spell of weeping, or a debauch of sympathy and concern over the troubles of some one of the many members of her family When she was heard from a few months later, she was able to report much improvement In three months she had had only four attacks, one after a nervous shock, one after going on what she said was a wild party, one with a cold, and one just before menstruating

Case II.—An educated, prosperous-looking Jewish merchant, forty years of age, came to the clinic complaining of violent attacks of intense abdominal pain which he had been experiencing for fifteen years These began when he left college and went into business with his father Every few weeks he had been prostrated with an attack which, according to the history as first obtained, took the following course first there came mental depression, then lassitude, irritability, and one or two loose bowel movements, then abdominal soreness with peristaltic unrest, bloating and belching and finally severe pain

It is doubtless significant that the situation of the pain in the abdomen varied widely with the attacks The distress was usually intermittent and rhythmic, it got worse and worse, until finally it became so unbearable that the patient had to have a large dose of morphine to get relief There was no vomiting except that which was produced by the morphine Following the attacks, he was weak and exhausted and had to remain for two or three days in bed Between spells, his health and his digestion were good

We were helped by learning that in spite of the fact that for fifteen years this man had been having these attacks, his general health had remained good, and no great disaster had come to him, unless one should list under disasters four unavailing abdominal operations First, he related, the appendix was removed, later he parted with the gallbladder which was said to contain a

few small stones Apparently they were silent because their removal had no influence on the syndrome

The man was studied extensively by prominent internists but no one ever found a definite cause for the pain or a way to prevent its coming As a result the patient became more and more apprehensive about his future he greatly feared cancer and he felt that anything so severe as his disease must eventually put an end to his life

Our examination at the clinic failed to throw any light on the situation The man's duodenum was infested with giardia but, as we expected, their removal did not have any influence on his health

Repeated questioning finally brought out the fact that the attacks followed some emotional storm Like so many men of his race the patient could stand with equanimity large financial losses but small ones attributable to the carelessness and inefficiency of employees would often send him into a towering rage from which he would emerge weak and shaky and so ill that he would have to be taken home There the painful aspects of the attack were soon upon him

When we turned to the wife for her opinion regarding the origin of the disease she stated in no uncertain terms that if her husband could only learn to restrain his temper there would be no more spells Finally the man admitted that this was probably correct and he and his wife agreed that there never had been an attack during a vacation or when he was away from the store Later the man confessed that one reason for the violence of his explosions was that he hated his small town business but did not know of any way of escaping from the trap which his family with the best of intentions had built for him

The man left promising to reform and be good but apparently his resolutions could not be kept and from a letter recently received we learned that he has had several falls from grace with the usual dire results

Obviously the diagnosis in cases like the two here reported must be made on the basis of a history good enough to reveal the important happenings which precede the attacks It is not difficult to see why the patient, of himself and without urging rarely mentions these details which are not to his credit The physician is likely to hear of them only if, in these cases his experience leads him to suspect the nature of the attacks, and even then he may have to talk to some member of the family before he can get at the truth

It is essential first to recognize the fact that the syndrome is not such as is likely ever to be produced by known diseases such as intestinal obstruction appendicitis peptic ulcer, cholecystitis diverticulitis pancreatitis kidney stones nephritis spondylitis or angina pectoris An important point is that the

pain comes without relation to any part of the digestive cycle or to defecation, menstruation, urination, or bodily exertion Another helpful point, often, is that there is little if any indigestion or discomfort between spells, in fact, even in spells there may be no sign to indicate that there is irritation of, or obstruction in any part of the digestive tube Still another helpful point in some cases is that the pain moves about in the abdomen, showing that it has no constant point of origin, and another point which is helpful in long lasting cases, is that during the course of years the patient does not come to any bad end If the disease were in the appendix, the gall-bladder, or the ureter, or if the pain were attributable to an internal hernia, the pitcher could hardly keep going to the well month after month and year after year without getting cracked, new symptoms and complications eventually would appear, and the diagnosis would become simple

Finally, if the patient is nervous, worrisome, temperamental and Jewish, the physician should be particularly reluctant to start on a course of optimistic but probably useless operating

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THE MOST IMPORTANT FEATURE IN THE MANAGEMENT OF CHRONIC ULCERATIVE COLITIS, MANAGEMENT FOLLOWING PERFORATION IN A CASE OF DIVERTICULITIS, TWO INTESTINAL CARCINOMAS IN THE SAME CASE OF CHRONIC ULCERATIVE COLITIS AND THE MANAGEMENT OF THE RESULTING OBSTRUCTION

J. ARNOLD BARGEN AND ROBERT J. COFFEY

THE MOST IMPORTANT FEATURE IN THE MANAGEMENT OF CHRONIC ULCERATIVE COLITIS

Case I.—A male medical student aged twenty-five years was admitted to the clinic March 17, 1934, complaining of diarrhea of four and a half years' duration. At the onset acute watery diarrhea suddenly had developed while the man had been in the forest service. At the same time many of his associates had had a similar condition. He had continued to have about six watery stools daily, containing pus and at times he had passed small amounts of bright red blood. Frequently there had been associated dull abdominal pain and griping. Symptomatic treatment had been ineffective. In spite of this condition the man had returned to school and had suffered no loss of weight. In June, 1933, fever had developed, also more severe bloody diarrhea had appeared, and the man had been confined to bed for a month. During this exacerbation he had lost 30 pounds (about 14 kg.), but recovery had been rapid enough to permit his return to school in September, 1933, although he had continued to have eight to ten stools daily. Following the Christmas holidays, during which he had failed to secure his accustomed rest, an exacerbation had developed, and the trouble had continued to the time of the patient's admission.

When we examined the young man, he was surprisingly well nourished, weighing 167 pounds (about 75 kg.). On general examination the only notable findings were tenderness, grade 1, across the lower part of the abdomen, and tenderness, grade 2, on rectal examination. A thorough search for foci of infection gave negative results. Studies of the blood, including a flocculation test, were negative, except that fifty-three filamented leukocytes were counted, as compared to twenty nonfilamented leukocytes. Studies of the stools failed to reveal the presence of the Mycobacterium tuberculosis or of the dysentery streptococcus of chronic ulcerative colitis. On proctoscopic examination the mucosa was granular and bled easily as far as it could be examined. Activity of the disease was graded [illegible] An anal ulcer on the left side was noted

Roentgenoscopic study of the large bowel disclosed that advanced chronic ulcerative colitis extended its entire length

After injections of specific antibody solution twice daily for three weeks, the man was able to leave the hospital and return home His diarrhea had abated considerably and his weight was 181 pounds (about 82 kg), representing a gain of 15 pounds (about 7 kg) Arrangements were made for regular vaccine therapy to be administered at home

This is an average case of chronic ulcerative colitis with rather extensive disease, and we chose the history for presentation for several interesting reasons In the first place all who have followed what might be called the controversy on chronic ulcerative colitis must realize that small differences in handling cases might account for differences of opinion

Here is a young man who failed progressively, a medical student under the care of an excellent metropolitan clinician, but who, in spite of the fact that the usual causative organism was not found, is making satisfactory progress under his present treatment He received intensive treatment with the specific antibody solution (concentrated serum) given intravenously He was at the clinic three weeks, gained greatly in weight, and felt like a different fellow We allowed him to go, not back to school, but home, where he will continue on a rigid, protracted regimen

This brings up what would seem to be the most important feature of the management of colitis A protracted, well-ordered program of treatment gives the best results This disease should be regarded as is tuberculosis That is, as a severe, destructive, chronic infectious process This is not a mucosal disease but a disease of the intestinal wall There is a long-standing destructive process, and to reverse that process takes time and continuous effort As soon as the patients begin to improve, it is important to feed them generously, which means 3000 calories, of a high-calorie, high-protein, low-residue type of diet The greatest difficulty comes in trying to feed these people When we explained to this patient that food was part of his medicine he pushed himself to eat Forced feeding, if you want to call it that, is, we think, an important feature in the management of these

cases The follow up treatment with vaccine is important We looked for amebas, as we do in all of these cases, but we found none in the rectal discharge

We are glad the patient in the case reported did not receive arsenic, for example treparsol or stovarsol, for although these drugs may help in a few of these cases they cause trouble in a great many more If these drugs are given it is important to give them only at a certain stage of the disease, when bleeding has stopped Giving a quantity of arsenic, as you do for amebiasis, frequently causes trouble. Tincture of iodine seems to help about 10 to 15 per cent of these people

The young man whose case we have presented is going to spend his energy this spring and summer trying to get well He will go home, take things easy, eat, sleep, keep regular hours, and continue with the vaccine in the hope that he may go back to school next fall He will be back in three months and we will make another roentgenologic and proctoscopic examination We expect his colon to widen out We think this depends in part on how much destruction has taken place, but also on persistence of treatment Failure in the management of these cases often depends on failure to understand the pathologic process in this disease

Dr Rynearson In what percentage of cases of chronic ulcerative colitis do you fail to find the diplococcus? Dr Barker In about 20 per cent There are undoubtedly some cases in which if search was continued long enough the organism would be found

Dr Rynearson Do you get about the same percentage of improvement in that 20 per cent as in the other 80 per cent? Dr Barker My impression is that that question should be answered "yes"

Dr Rynearson What are your figures? Dr Barker About 75 per cent of our patients become clinically well Relapses result from many causes We have reviewed 209 cases in which relapse occurred Fifty seven per cent of the relapses occurred in association with infection of the upper part of the respiratory tract That alone would suggest the relation hip

between infections of the upper part of the respiratory tract and this disease

Dr Rynearson Just one other question I have read some articles that have been largely destructive and I wonder what they have to offer Dr Bargen The best answer seems to be that the critic sees few cases, and so far no one has offered anything that affords even remotely comparable results One of these critics describes a disease which begins above the lower part of the rectum In 95 per cent of the cases we see, the disease starts at the anus, in the other 5 per cent, the disease is of patchy distribution

Dr G E Brown Take a group of 100 cases followed five years or longer, what would be the outcome? What would happen? Dr Bargen If the patients had this sort of treatment, and had no complications, they would be well I reviewed ten years of treatment, showing the changing results and the reduction in mortality In 1920 we saw 57 patients, 16 of whom underwent ileostomy Seven died following ileostomy Last year (1933) we did not do a single ileostomy for chronic ulcerative colitis and had only one death

Dr Helmholz I want to ask regarding contracture of the bowel, sclerosis of the muscle Have you gone into that at all, and the chance of recovery from it? Would you say that with staining, you can show that muscle actually had been destroyed? Dr Bargen In some cases, although the walls were markedly thickened, and fibrosed, they later returned to normal We have had several cases in which the wall of the bowel has returned absolutely to normal, grossly and microscopically This has been discussed in a paper by Dixon and me on "Cancer in association with chronic ulcerative colitis" Muscle seems to have been destroyed or replaced

Dr Helmholz As long as mucosa remained, restoration could take place

The man returned to the clinic in September, 1934, at which time his weight was 208 pounds (94 kg) His stools were reduced to three or four daily, and he had noted blood only twice in the preceding six months The activity, as seen

on proctoscopic examination was markedly reduced, and on roentgenoscopic examination of the colon improvement was evidenced by a distinct widening of the lumen of the bowel At the time of this visit the man was returning to medical school, and he was advised to continue with the vaccine therapy

MANAGEMENT FOLLOWING PERFORATION IN A CASE OF DIVERTICULITIS

Case II.—A farmer fifty two years of age came to the clinic April 3 1934 for repair of an abdominal fecal fistula He recalled that he had had an attack of severe pain in the left lower region of the abdomen in 1931 which had led to the diagnosis of renal colic Cystoscopic examination at the time had given no relief and the pain had disappeared spontaneously after one week In January 1932 pain in the left lower abdominal region again had developed associated with constipation Following an enema the pain had become excruciating and the man had been rushed to the hospital and exploration had been made immediately A ruptured diverticulum of the sigmoid and peritonitis had been found Drains had been inserted and the abdomen closed Following that the operative wound had broken down and purulent fecal drainage had developed and had continued The amount of fecal material passed through the fistula had been small On several occasions, drainage had ceased and immediately the patient had complained of considerable lower abdominal discomfort In April 1933 an unsuccessful attempt at closure of the fistula had been made

The man appeared to be in good general condition and was of normal weight. A small draining fistula was present in the old operative scar in the lower part of the abdomen Otherwise physical examination gave negative results Studies of the blood did not disclose anything abnormal nor did roentgenologic examination of the thorax The only notable finding on proctoscopic examination was lack of normal mobility of the sigmoid Roentgenoscopic study of the colon revealed diverticulosis of the descending colon and of the sigmoid with definite diverticulitis and narrowing of the lumen of the middle loop of the sigmoid The communication of the sigmoid with the fistula was demonstrated Sulphur bodies or Mycobacterium tuberculosis were not demonstrated in scrapings from the fistulous tract.

A temporary transverse colonic stoma was made one week after the patient's admission and he was dismissed several weeks after operation

He returned in September 1934 and at that time stated that the fistula had been closed for the past three months The stoma had been functioning satisfactorily and the man felt well Roentgenologic examination of the colon by roentgenoscopic means gave evidence of the diverticulosis and slight hypertrophy of the sigmoid but there was no obstruction at this point There appeared to be a slight impairment of emptying of the rectum Failure of fistulous communication was not demonstrated The patient was advised to return in three months for the removal of the [illegible] and in the meantime to continue with [illegible] with a resolution of the [illegible]

The man's progress was uneventful, and on his return further improvement of the condition of the sigmoid was reported on roentgenoscopic study Clamps were applied to the intervening spur between the ends of the colon, December 8, 1934, and two weeks later intraperitoneal closure of the stoma was carried out The postoperative course was mild and without complications The man was dismissed in several weeks, with instructions to continue to follow a bland diet and to take mineral oil daily in order to maintain softness of the stools

We think about 15 per cent of patients who have diverticulitis come to surgical operation Most cases of diverticulitis and, we think, all cases of diverticulosis are medical problems, and the management follows very simple lines

This case is an example of what may happen The patient got along apparently well until he had a perforation Later an attempt was made, elsewhere, to close the resulting fistulas, with the usual lack of success when previous colostomy is not performed Well, it seemed obvious that these would not heal without some surgical procedure, so Dr Dixon performed a colostomy several inches above the lesions The stoma was closed months later, after healing had occurred

Dr G E Brown You say 15 per cent of patients who have diverticulitis come to surgery? Dr Bargen Approximately

TWO INTESTINAL CARCINOMAS IN THE SAME CASE OF CHRONIC ULCERATIVE COLITIS AND THE MANAGEMENT OF THE RESULTING OBSTRUCTION

Case III —A married woman, aged thirty-one years, was admitted directly to the hospital, April 23, 1934 Following scarlet fever, at two years of age diarrhea had developed, and had continued steadily thereafter The woman usually passed six to eight watery stools daily, and small amounts of blood at times This, however, failed to affect seriously her general health, for she had gained weight, had attended school, and had led a fairly normal life In October, 1933, the amount of blood in her stools had increased, pallor had become marked, and at times her abdomen had become distended In addition, lower abdominal cramps had become annoying Edema of the lower extremities, and dyspnea, had developed several months later, and she had consulted a physician in January, 1934, who had advised that she remain in bed Measures to improve her general health and to correct the anemia had been instituted However, little improvement had resulted, and for two to three weeks before her admission she had vomited several times daily

She was emaciated and obviously anemic Her temperature was 99 6° F, and her pulse rate 110 beats per minute The entire abdomen was tender,

grade 1 and the descending colon was palpably rigid and tube like. Pretibial edema grade 1 was present On pelvic examination a tender mass was palpated in the left culde-sac which was thought to be independent of the internal genitalia The concentration of hemoglobin was 8.5 gm per 100 c.c. of blood and leukocytes numbered 11 400 per cubic millimeter of blood Albumin grade 2 was present in the urine and the concentration of blood urea was 51 mg per 100 c.c

The evening after admission the woman suddenly complained of severe pain in the left lower part of her abdomen which was followed by vomiting localized muscular spasm with tenderness and a weak, thready pulse. It was thought that she had a complete perforation of the large bowel and conservative measures were instituted There was decided improvement for the next two days Further blood chemical investigations at that time gave the following results 72 mg of urea per 100 c.c of blood 8.8 mg of calcium per 100 c.c. of serum, and carbon dioxide combining power 43.8 volumes per cent.

Four days after admission acute phlebitis developed involving the left short saphenous vein and femoral veins and then forty-eight hours later the right short saphenous became inflamed A decided tendency to thrombosis after intravenous injection of glucose was noted Proctoscopic and roentgenoscopic examinations of the bowel were omitted in view of the patient's extreme condition One week after admission the pain in her left leg and thigh became worse and the extremity became edematous discolored and cold. It was apparent that there was massive venous occlusion The temperature remained only slightly elevated In a few hours the pain in the left lower part of the abdomen recurred and after a brief period the patient died

At postmortem examination the entire large bowel was involved in the chronic ulcerative disease and in addition there were two superimposed carcinoma one of the splenic flexure and the other of the sigmoid

This is a cursory review of a very interesting story, but we could not investigate further because the patient always was too sick We do not often see colonic perforation right under our eyes

The woman was in a state of shock had cold and clammy extremities and an acute pain, and a very large mass developed which felt like feces outside of the colon We did the thing which we think is most important in a case of obstruction and that is stop giving anything by mouth We also elevated the foot of the bed gave morphine and within five days the condition subsided and the mass became smaller Then we began to give small amounts of food by mouth The important factor in the history seems to be the long-continued diarrhea Did she have ulcerative colitis for thirty years? When he died she had two carcinomas and involvement of the ileum.

The ileum ran right into the colon without any particular line of demarcation We have never seen this before and Dr Robertson, of the Section on Pathologic Anatomy, said he never had seen it Chronic ulcerative colitis involved the entire colon There was an annular, scirrhous type of carcinoma, with perforation and formation of abscess at the splenic flexure, and in the sigmoid there was a polypoid carcinoma—two entirely different types of growth This is the thirtieth case in 1,500 cases of chronic ulcerative colitis which we have seen in which carcinoma appeared in the course of long-standing chronic ulcerative colitis In about seven or eight of the cases there were multiple carcinomas, in several cases, literally hundreds of them Most of the patients who had carcinoma were young, the youngest was nineteen years of age

Dr G E Brown How active was that colitis? Dr Bargen Fairly active

Dr Wilbur Did you think the diarrhea might have been attributable to anatomic defect? Dr Bargen In part, perhaps, but of course the patient had the infection, and the ileocecal incompetence here seems attributable to the massive long-standing colitis

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REGIONAL ULCERATIVE ENTEROCOLITIS

J ARNOLD BARGEN AND ROBERT J COFFEY

Various ulcerative diseases tend to afflict certain portions of the intestine Thus, chronic ulcerative colitis involves the distal portions, including the rectum, in approximately 95 per cent of cases of this disease Amebiasis usually involves the cecum and ascending colon, and the site of predilection of tuberculosis is the ileocecal coil However, it is common for an ulcerative disease to involve the entire colon, or, as in chronic ulcerative colitis, a large, distal portion of it

We are presenting this morning a group of cases that are examples of a rather infrequent, patchy, or segmental distribution of ulcerative processes of the lower part of the intestinal tract We wish to emphasize the diverse situations of the diseased segments, the subsequent destruction of the bowel the inevitable cicatricial narrowing and, in addition, we wish to suggest the surgical maneuvers that might be indicated for relief

CASE I.—A railroad conductor aged forty six years, visited the clinic August 14 1934 complaining of diarrhea and severe loss of weight One year before diarrhea had developed and had been associated with severe abdominal cramps The diarrhea gradually had become worse and the man had passed as many as twenty five stools daily but he never had noted the presence of blood Weakness had become so marked that he had been confined to bed In about three months the diarrhea had lessened but the abdominal pain and weakness had persisted His condition had remained unchanged in spite of various forms of treatment including a course of autho is serum. Three months before his admission his appetite had failed Nausea occasionally had resulted after eating and he had persistent definite abdominal distention at times In the past few weeks he had been having two to five large bulky loose stools daily Occasionally small amounts of frequently small or large quantities of blood usually present In addition there had been severe cramping pain also at the umbilicus

On first examination, we were struck by the apparent evidence of marked loss of weight, the patient had lost 60 pounds (about 27 kg), he said His complexion was that of a person in poor health The abdomen was slightly distended and flaccid Marked tenderness was elicited below the umbilicus Beginning in the same region, and extending to the right iliac fossa, a ropy thickened structure could be palpated

Of interest in examination of the blood was a count of 40 nonfilamented leukocytes, as compared to 18 filamented leukocytes No Mycobacterium tuberculosis, and no diplostreptococci of colitis were found in the stools Roentgenologic examinations of the chest gave negative results, those of the colon revealed diverticulosis of the entire colon Roentgenologic examination of the small intestine after a barium meal was then made, and evidence of diffuse,

Fig 34.—Case I Inflammatory lesion of terminal part of ileum

terminal ileitis was clearly demonstrated, in addition, a more proximal segment of the ileum was involved (Fig 34)

The patient was hospitalized, and a medical regimen was continued for several weeks, but without benefit Abdominal cramping and distention persisted, as did vomiting The man passed several foul-smelling stools daily

In view of the recurrent, although partial, intestinal obstruction and profound nutritional disturbance, the abdomen was opened October 9, 1934 The terminal 3 feet (91 cm) of the ileum were thickened and edematous, and there was mild involvement of the cecum At a distance of about 2 feet (about 61 cm) from the ileocecal valve, a small, hard mass, measuring 3 by 2 cm., was palpated in the ileum, at its mesenteric border The ileum was divided proximal to the thickened portion a wedge-shaped piece was removed, the distal end was inverted and the ileum was attached to the transverse colon

Pathologic study of the resected piece of ileum suggested chronic inflammation and in only one section of many examined was a tiny lesion suggestive of tuberculosis found (Fig. 35).

The postoperative course was uneventful and the man was dismissed in three weeks having gained weight and strength and no longer complaining of abdominal cramps. He was sent to a sanatorium in New Mexico and in a letter dated February 1935 the patient stated that he felt well was eating well, and had gained 18 pounds (about 16 kg.).

The foregoing case is very suggestive of so-called "regional ileitis," a condition which only recently has received intensive

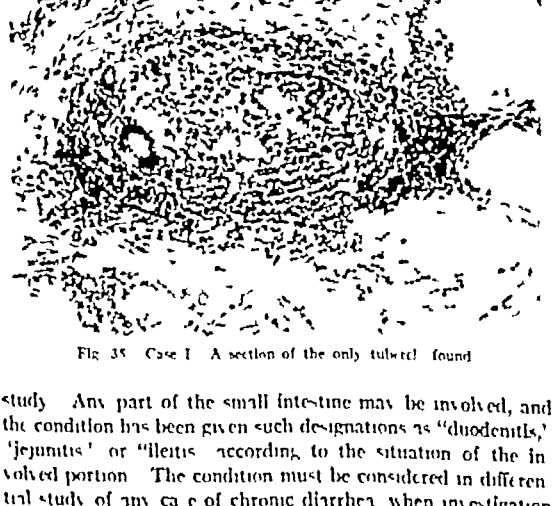

Fig. 35. Case I. A section of the only tubercle found.

study. Any part of the small intestine may be involved, and the condition has been given such designations as "duodenitis," "jejunitis" or "ileitis" according to the situation of the involved portion. The condition must be considered in differential study of any case of chronic diarrhea when investigation of the colon gives a negative result. Abdominal cramping is a frequent complaint and the stools are characteristic in that they are large, mushy, and of an offensive odor. The etiology is unsettled. Recent investigations have shown that the earlier

conceptions that a tuberculous infection is present in such cases, hold only in a small percentage of them However, in view of the finding of one lesion resembling a tubercle in innumerable sections studied, one wonders in how many others tuberculosis would be found if search was made as persistently as it was prosecuted in this case In view of the pathologic change, which consists of mucosal inflammation and ulceration, involvement of the entire wall of the bowel, and subsequent narrowing, the relationship of the condition to chronic ulcerative colitis, in which the same changes occur in the colon, must be considered Because of the tendency toward perforation, with formation of fistula, and because of the tendency to obstruction, operation is indicated in most of these cases A short-circuiting procedure is the one of choice, resection is occasionally indicated

Case II—A man, aged twenty-two years, came to the clinic October 23 1932 Six months previously abdominal pain and diarrhea had developed, and gradually had become more severe A month before the patient came to the clinic appendectomy had been performed, but the diarrhea and pain had persisted as before Blood had appeared in the stools in moderate amounts For several weeks before the man's admission, the number of stools had become reduced to three or five daily, but the abdominal pain, which occurred in paroxysms lasting ten to sixty minutes, had become worse

The man was pale and emaciated, he weighed 116 pounds (about 53 kg) Rectal narrowing and tenderness were noted The temperature was 100° F and the pulse rate 110 beats per minute Mild secondary anemia was present. Proctoscopic examination revealed an anal fissure Roentgenologic studies of the colon disclosed extensive ulcerative colitis, with marked mucosal destruction of the large bowel proximal to the splenic flexure (Fig 36) Since the situation of the involvement suggested the possibility of tuberculous colitis, thorough studies for tuberculosis were made, including a roentgenologic examination of the chest, and examinations of stools, but Mycobacterium tuberculosis was not found The diplostreptococcus of colitis was not isolated

While the patient was in the hospital, a perirectal abscess developed and, under the influence of conservative measures, it opened and drained After a liberal course of the specific antibody solution had been given, the man was dismissed, and arrangements were made for administration of vaccine at his home

July 3, 1933, the patient returned for reexamination, at which time he was having two or three formed stools daily, and felt much better Progress was satisfactory until January, 1934, when an exacerbation of his trouble occurred He returned to the clinic a month later, at which time there was a mass in the right lower abdominal quadrant Roentgenologic study suggested

that the disease process was confined to the same part of the bowel as that to which it had been confined on previous examination and evidence of deep penetrating ulcers was reported. The acute symptoms subsided after a week's treatment with the specific antibody solution. Recurrent attacks of obstruction made operation advisable. April 4, 1934, end to side anastomosis of the ileum and the sigmoid was made. The colon was found to be thick and edematous, and a small amount of turbid fluid was present in the peritoneal cavity. Examination of the fluid was negative for Mycobacterium tuberculosis. The pathologist examined a wedge-shaped piece of ileum that was re-

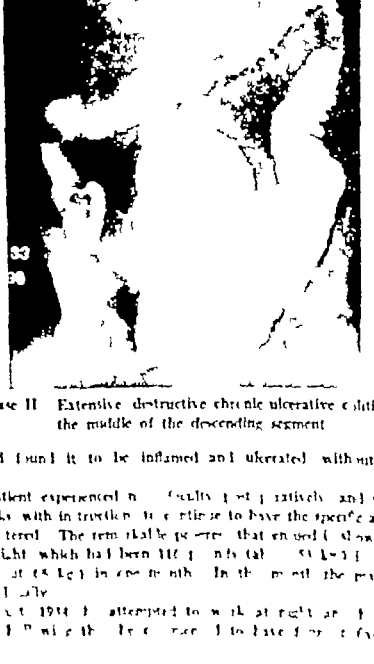

Fig. 9.—Case II. Extensive destructive chronic ulcerative colitis proximal to the middle of the descending segment.

moved and found it to be inflamed and ulcerated without evidence of tuberculosis.

The patient experienced no difficulty in getting relatively and was discharged in two weeks with instructions to receive the specific antibody solution at intervals. The remarkable recovery that ensued is shown by the fact that his weight, which had been 117 pounds (53 kilograms) on April 3, rose to 149 pounds (67.6 kilograms) in one month. In the month the patient received only

In August 1934 I attempted to walk at night and [illegible] three [illegible] I [illegible] to take [illegible]

daily At a visit to the clinic in October, 1934, he appeared to be greatly improved and felt well The lowest 3 cm of rectal mucosa bled more easily than normal on proctoscopic examination and the draining anal sinus persisted Roentgenologic study of the colon disclosed that the ulcerative process was limited to the part of the bowel which was proximal to the middle of the descending colon, the condition of this portion of the bowel was much improved, and the anastomosis was functioning freely

The foregoing case is of unusual interest from several standpoints It has been noted that chronic ulcerative colitis usually commences in the rectum, and extends upward Consequently, it is not common for involvement of the ascending and transverse colon to occur unaccompanied by rectal pathologic change Such a distribution is more characteristic of tuberculous or amebic colitis Since the sigmoid and rectum were spared, this is one of the rare cases of chronic ulcerative colitis in which the surgical procedure employed has been indicated It must be remembered that at the time of writing this report the patient was by no means cured, and that the ulcerated bowel still remains For this reason, specific therapy is to be continued for some time Another instructive point to be emphasized by this case is the management of perirectal and anal abscesses in a case of chronic ulcerative colitis Conservatism and a hands-off attitude are imperative Extensive incisions and excisions invariably result in spreading cellulitis, destruction of perirectal tissue and great scarring

Case III.—A married woman, aged forty-one years, visited the clinic, August 27, 1934, in quest of surgical repair of a draining sinus in the left groin Her trouble had started with an attack of severe, bloody diarrhea, associated with abdominal cramps, in 1926 At that time, hemorrhoidectomy and cauterization of prolapsed rectal mucosa had been performed Relief had not followed, and the woman had continued to pass ten to fifteen loose, bloody stools daily Since she had become progressively weaker and more toxemic and had lost 30 pounds (about 14 kg) appendicostomy had been performed, and irrigations through the stoma had been carried out The diarrhea then had lessened, and the woman had regained strength and weight After several months the appendix and the tip of the cecum had been removed

In 1927, severe recurrence of the diarrhea had developed, at which time gas had been passed through the vagina Her attending physician had found a rectovaginal fistula She then had enjoyed a remission of six years, during which time she had felt well, and she never had had more than three stools in twenty-four hours

Again one year before her admission to the clinic, a severe attack of diarrhea had developed and the conspicuous feature on this occasion had been the persistent and intense pain in the lower left part of the abdomen. After several months an abscess had pointed in the left lumbar region; this immediately had been incised and profuse purulent drainage had resulted. Relief of pain had followed and the discharge had continued until March 1933, when the sinus had closed. After a few weeks the abscess had reformed at the same point, and again had been opened. Closure again had been complete in two months. In June 1934 swelling and localized tenderness had appeared just above the middle of the left iliac crest and this new abscess had been incised from the site purulent material, fecal matter and gas had been expelled.

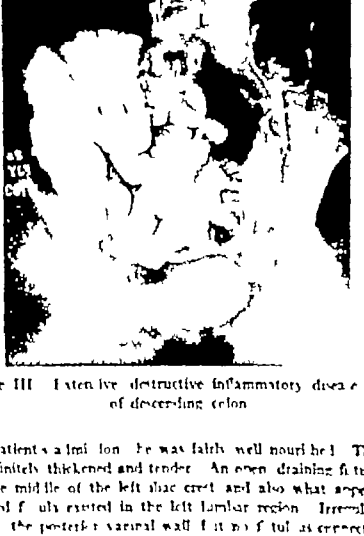

Fig. 17.—Case III. Extensive destructive inflammatory disease of a segment of descending colon.

On the patient's admission he was fairly well nourished. The descending colon was definitely thickened and tender. An open draining fistula was found just above the middle of the left iliac crest and also what appeared to be a recently healed fistula existed in the left lumbar region. Irregular induration was felt along the posterior parietal wall but no fistulous connection with the rectum could be demonstrated.

Complete studies of the blood and gastrointestinal examination of the first case negative results. The purulent material and scrapings from the fistulous tract contained no specific bacterium but were positive for the

stomach Roentgenologic examination of the small intestine gave negative results The rectum was examined proctoscopically for 24 cm , but a fistulous opening was not observed The anus was scarred and contracted Roentgenologic study of the colon revealed a deformity, with marked narrowing involving the distal part of the descending colon and the proximal part of the sigmoid The involved portion was about 12 cm long, and a fistulous tract, which originated in this portion, was visualized (Fig 37)

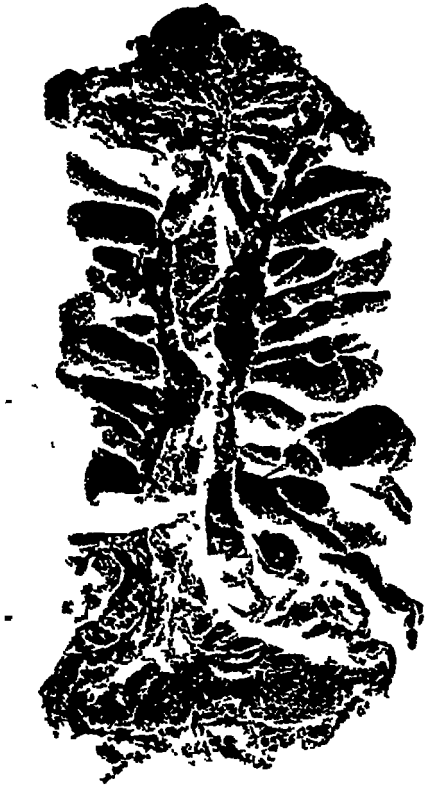

Fig 38 —Case III The resected portion of colon

September 5, 1934, exploration was performed, with the patient under spinal anesthesia, and a localized region of chronic ulcerative colitis, involving the lower part of the descending colon and the proximal part of the sigmoid was found This portion of the bowel was freed, was brought out onto the surface of the abdomen, and was removed by an exteriorization type of procedure Study of the specimen confirmed the diagnosis of chronic ulcerative colitis, and multiple pseudopolyps were found (Figs 38, 39)

The postoperative course was mild and seventeen days later clamps were applied to the spur intervening between the sections of the double-barrelled colonic stoma Two weeks later about half the fecal current was being passed by rectum and the woman was dismissed She reported in a letter written in February 1935 that there seemed to be no tendency toward spontaneous closure of the stoma and she is to return soon for intraperitoneal closure.

In the foregoing case, the inflammatory disease seemed to be limited to a segment of the descending colon However, the involvement here was very severe, multiple perforations and

Fig 39—Case III Wall of resected portion of colon with an inflammatory polypoid mucosal ta-

sinuses were present The question in cases of this sort al ways comes up, whether the disease has its inception in the involved segment of bowel Furthermore, although local resection seems the treatment of choice in these cases, doubt remains as to whether the disease will recur in the other portions of the large intestine Up to the time of writing of the report, recovery had been uneventful Pathologically, this is the same type of infection as that which begins in the rectum and spreads upward

Case IV —An unmarried woman, aged thirty-seven years, was admitted to the clinic July 12, 1934 Her complaint was of diarrhea that had commenced fifteen months before, following extraction of infected teeth At the onset, the diarrhea had been mild, but after a few months blood had appeared in the stools which then had numbered ten to fifteen daily She had had a septic type of fever, had lost considerable weight, and had complained of generalized abdominal pain and painful defecation She had become anemic, and several transfusions of blood had been given A fibroid uterus had been removed, inasmuch as it had been thought that this was responsible for some of the pain She had been a patient in several sanatoriums, but bloody diarrhea, complicated by slight anal incontinence, had persisted She had been operated on for anal fistula For most of the time since the onset of her trouble she had been confined to bed On admission, the woman weighed 84 pounds (about 39 kg) and was moderately emaciated She complained of tenderness in the region of the descending colon The perianal tissues were markedly scarred, and digital examination of the rectum was extremely difficult for the physician and was painful to the patient, because of the marked narrowing which involved the rectum as far as it was examined Flocculation tests for syphilis gave negative results and the concentration of hemoglobin was 10 gm per 100 cc of blood In the blood smear, 50 nonfilamented cells were found as compared to 10 filamented cells The sedimentation rate was 111 mm in one hour Roentgenologically, the chest was negative Roentgenologic examination of the colon revealed marked narrowing of the rectum, and two regions of ulcerative colitis, with marked narrowing of the lumen, one was at the hepatic flexure and the other, at the splenic flexure (Fig 40) The anus was scarred in its anterior quadrant, and was incompetent, grade 2 There was a draining sinus on the left side and a similar one on the right, and there was an annular stricture 3 cm above the anus, above which the mucosa appeared to be normal

The patient was hospitalized and immediately was given specific antibody solution intramuscularly twice daily She also was given a liberal diet Her progress was not at all satisfactory Since her appetite was very poor, it was only after persistent urging that she consumed her minimal caloric requirement She continued to run a low-grade septic type of fever and failed to gain weight It was decided that operation was not indicated at the time, and that if medical measures failed after a long trial, ileostomy might become necessary The patient returned home after two months, at which time she commenced to gain weight, the stools contained no blood, and her appetite had improved Arrangements were made for her to receive the anticolitis vaccine twice weekly, and instructions aimed at increasing weight and improving her general condition were outlined

In the foregoing case, the destructive infection had a segmental distribution, although practically the entire colon was somewhat involved Nothing short of complete exclusion of the large intestine would have been of value from the surgical standpoint Hence, we feel justified in doing everything pos-

sible from the medical standpoint first If this fails, as long as the patient is making some improvement ileostomy always can be performed

COMMENT

This group of four cases illustrates the variable severity with which ulcerative processes of the intestine affect different segments In the first case, the terminal part of ileum and

Fig. 40—Case IV The irregular distribution of the ulcerative disease and stricture like narrowings near the hepatic flexure splenic flexure descending colon and rectum.

the cecum only were involved, in the second case the ascending transverse and part of the descending colon in the third case, a portion of the descending colon, and in the fourth although the entire colon was involved the severe infection with destruction of tissue had a segmental distribution In general management in all of these cases should be similar, including the greatest possible rest for the involved portion of bowel, with adequate systemic treatment to control the infection

This is not accomplished best by ileostomy, for although in theory such an operation would accomplish the object, yet in actual practice, intestinal destruction with shrinkage of lumen continues, so that rarely does healing progress to a stage at which an ileac stoma finally can be closed Furthermore, ileostomy carries considerable risk Cecostomy has little or no value in these cases, for allowing part of the intestinal content to pass over the lesion is just as bad as allowing all of it to do so Complete resection, or short-circuiting, together with adequate medical care, are the measures of choice In cases of this type, cooperative management by internist and surgeon have the greatest value

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ABDOMINAL HODGKIN'S DISEASE REPORT OF A CASE

J ARNOLD BARGEN AND HAROLD C OCHSNER

The so-called "abdominal type" of Hodgkin's disease occurs rather infrequently Minot and Isaacs, however, found that in 25 per cent of 477 cases the initial symptom was suggestive of an abdominal lesion When primary involvement is in the abdomen, the difficulty of diagnosis is greatly increased Bunting has said that of all the forms of Hodgkin's disease those of primary involvement in the abdomen are most obscure The case we wish to present illustrates this primary involvement of abdominal structures, in addition, however, some of the characteristic manifestations of Hodgkin's disease were present, which aided in making the diagnosis

The patient a man thirty years of age was brought to the hospital in an ambulance April 6 1934 He complained of weakness anorexia jaundice and loss of weight He had been quite well until February 1933 when he had slipped while lifting a heavy load of coal and had trained his back" In May 1933 he had noticed what he had thought to be a hernia in the right groin he had felt a lump the size of an egg in this region when in a reclining position but it had seemed to disappear when he stood up He had given this manifestation little consideration and had continued his usual activities working as a watchman on steam ships About Christmas time 1933 itching of his soles had been quite troublesome and shortly afterward he had had weakness night sweats and fever which had been his best in the evening Anorexia soon had developed weakness had progressively increased and he had been troubled by insomnia The first week in February 1934 mild jaundice had developed

The patient was hospitalized elsewhere from February 9 to 18 It was found that there was an elevation of the level of serum bilirubin and a diagnosis of hepatitis was made During the period of hospitalization he had lost 30 pounds (13 kg) and had developed a pallor which gradually increased An afternoon temperature of 100 F with slight diurnal variations and night sweats and a severe pruritus developed Only occasional nausea and vomiting were noted In the latter part of March the right upper abdominal pain and abdominal

jaundice again appeared and with it, increasing weakness, anorexia, insomnia and constipation The temperature would be as high as 103° to 104° F in the afternoon, and it was high in the morning as well Early in April, the patient became somewhat deaf, and was mentally fogged

When admitted to the clinic, the patient was acutely ill and appeared to be very toxic His temperature was 103° F, his pulse rate 120 beats per minute, and his blood pressure in millimeters of mercury 90 systolic and 70 diastolic There was a mild degree of jaundice The area of mediastinal dulness was increased, but no other lymphadenopathy could be demonstrated with the exception of a firm, tender mass, about 2 cm in diameter, deep in the right groin The edge of the liver was just palpable, the spleen was not felt at the first examination Examination of the ocular fundi revealed atypical cotton wool patches in the retinas Examination of the blood revealed a moderate degree of anemia, the erythrocyte count varied from 3,530,000 to 3,580,000 per cubic millimeter and the value for hemoglobin from 8 4 to 8 7 gm per 100 c c Leukopenia was present, the count varying from 3,400 to 5,100 leuko

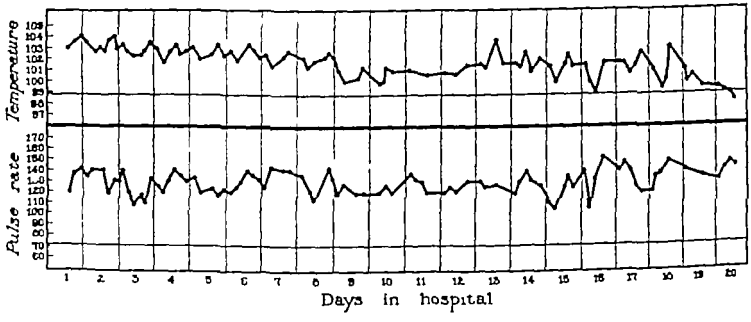

Fig 41 —Temperature chart

cytes per cubic millimeter The monocytes seemed relatively increased, comprising 15 per cent of the leukocytes No other significant morphologic changes could be demonstrated The values for blood urea and blood sugar were normal, but serum bilirubin was increased to 4 2 mg per 100 c c Urinalysis gave negative results except for albumin, graded 2, and occasional small amounts of bile The galactose tolerance test was positive, 6 65 gm of reducing substance were excreted No parasites, ova, or unusual bacteria were found in the stools, they were constantly brown in color and contained bile

During the patient's stay in the hospital, his temperature was constantly elevated (Fig 41) His pulse rate was always increased, and he was confused and sometimes irrational He was often incontinent of both urine and feces There was slow but progressive failure On April 20, to confirm the presumptive clinical diagnosis, a retroperitoneal lymph node was removed from the right inguinal region, microscopic section of this revealed lymphosarcoma of grade 4, Hodgkin's type Unfortunately, the condition of the patient was so poor throughout the period of observation that roentgen therapy was deemed inadvisable He died twenty days after admission

Postmortem examination revealed extensive hyperplasia of lymph nodes in addition to infiltration of the hilar and aortic nodes, there was involvement of several lymph nodes in the region of the common bile duct. Sections of these nodes revealed changes typical of Hodgkin's disease. Despite the presence of these large firm nodes about the common bile duct there was no evidence of obstruction, the duct was patent and was not dilated.

The liver, which weighed 2,035 gm., was smooth with the exception of numerous small subcapsular nodules; similar nodules were found here and there throughout the parenchyma. Microscopic examination revealed the hepatic cords to be atrophic. Throughout the liver there were numerous nodules which revealed changes typical of Hodgkin's disease. There were smaller collections of connective tissue, endothelioid cells, Dorothy Reed cells and eosinophils in the portal spaces.

The spleen was considerably enlarged, soft and weighed 95 gm. It contained numerous firm nodules, 1 to 10 mm. in diameter, disseminated throughout its substance. Sections gave evidence that the lymph follicles were replaced by the typical infiltrations of Hodgkin's disease; the normal architecture was partially destroyed.

Hodgkin's disease is relatively uncommon, and the occurrence of jaundice in this condition is even more unusual. Minot and Isaacs observed that some degree of jaundice occurs in 10 per cent of cases, although only 6 per cent of 401 patients who died from Hodgkin's disease exhibited demonstrable jaundice, and it was not observed as an initial symptom in any of the 477 cases. The jaundice observed in this disease is usually considered to be obstructive and secondary to the pressure on the bile ducts of enlarged nodes in the portal fissure. It may also occur as a result of extensive infiltration of the hepatic parenchyma by lymphomatous masses. There may occur, as in a case reported by Stahr and Symwoldt, infiltration of the walls of the bile ducts, with consequent stenosis. Barron has suggested that toxic effects on the cells of the liver are more important in the causation of jaundice than pressure on the large bile ducts.

In our case jaundice evidently was not, or at least not entirely, on an obstructive basis, for during the period of observation there was adequate evidence that bile entered the intestinal tract. Laboratory data were not conclusive, although with retention of serum bilirubin there was a direct van den Bergh reaction, which is sometimes taken to indicate the presence of obstruction in the biliary tract, and the galactose test

was positive, presumably indicating injury to the parenchyma of the liver We considered, however, that the jaundice was probably intrahepatic in origin in view of the constant pres ence of bile in the stools There was no history of exposure to hepatotoxic drugs and nothing to make us believe that the case was one of so-called "acute catarrhal jaundice", moreover, there was much evidence for Hodgkin's disease, so it was considered that the icterus was a manifestation of this condi tion

A variable degree of elevation in temperature has often been observed in cases of Hodgkin's disease, although it may run an afebrile course It is commonly considered that there are three types of fever The first is a continuous mild fever, with slight diurnal variations, and the second is a remittent fever with daily variations of 1° to 5° F , the peak of fever occurring in the afternoon The third and least common is an intermittent fever, there is an abrupt onset of hyperpyrexia which continues, except for slight daily fluctuations, for a period of a few days to two weeks, to be succeeded by normal temperatures, which may last a few days or months In this type, first described by Murchison but commonly known as the Pel-Ebstein fever, the same hyperpyrexia-apyrexia sequence may be observed again and again The case we report probably represents a fever curve of the first type, and although there was some diurnal variation, the fever was well sustained except in the last two days There was evidence that such a fever had been present for some months before the patient came under our observation

In addition, there are two other manifestations that deserve comment The patient had complained of pruritus at the onset of his illness, long before the occurrence of jaundice Pruritus is a common symptom of Hodgkin's disease, and frequently occurs early, even before the appearance of enlargement of lymph nodes There was a moderate anemia, such as is often found, particularly in the advanced stages Relative monocytosis was the only morphologic abnormality Watkins stated that the finding of a shift to the left of the neutrophils, together with a shift to the right of the monocytes, which are

increased in number, is often helpful in establishing the diagnosis of Hodgkin's disease

In summary, our patient was a young man who, some months after he had noticed an enlarged lymph node in the right inguinal region, had had a troublesome pruritus which had been followed by the appearance of a fairly sustained fever, jaundice, prostration, and, subsequently, by further lymphadenopathy On postmortem examination, there was extensive hyperplasia of the lymph nodes In addition to infiltration of the hilar and aortic nodes there was involvement of several lymph nodes in the region of the common bile duct Histopathologic examination of these nodes revealed changes typical of Hodgkin's disease

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RECURRENT, REACTIVATED, AND ANASTOMOTIC PEPTIC ULCER

ALBERT M SNELL, B R KIRKLIN, JOHN F PLUNKETT, AND MAURICE P FOLLY

Dr Snell At the seminar this morning we propose to take up the matter of recurrent reactivated, and anastomotic peptic ulcer, with special reference to the diagnostic features The subject is a more or less troublesome one and we bring it up chiefly because not many physicians have the opportunity to see any large number of these lesions These ulcers are the bugbear of gastro-enterologists and of surgeons alike and constitute one of the major unsolved problems in connection with gastro-intestinal disease The following cases are reported to illustrate some of the difficulties in diagnosis and treatment which these lesions present In spite of great conservatism in the selection of cases, the best possible surgical care adequate preoperative and postoperative treatment as well as serious attempts to regulate the habits and activities of the patient who is operated on these lesions are occasional sources of difficulty No criticism is intended of the surgical treatment these patients have received nor do we present a plea for either more conservative or more radical treatment

First to be considered are the general indications for surgical treatment of peptic ulcer at the clinic About one of each four patients is operated on chiefly because of the major complications of ulcer penetration perforation obstruction and hemorrhage A few patients receive surgical treatment because of their own preference or because of the economic handicap imposed by the distress of ulcer and by therapy The general surgical results are and have been good about 85 to

90 per cent of patients are symptomatically relieved and stay well, a few have minor complaints but are not under any particular handicap Questionnaires have been sent out repeatedly and the answers are invariably the same Many of these patients pay no particular attention to diet or to regulation of their habits A small percentage are conspicuous because they have severe, intractable lesions

Recurrent ulcers have formed after every known type of gastric operation How frequently they appear, depends on the criteria for diagnosis and on whose opinion you want to take The figures for anastomotic ulcers occurring after gastroenterostomy are put as low as 3 per cent by the protagonists of conservative surgical treatment, much higher figures are given by those who favor radical resection After pyloroplasty, similar variations are reported After partial gastric resection, a rate of recurrence as low as 0 5 per cent has been quoted by German authors

Why cannot we give a final answer to the question of how often ulcers recur postoperatively? It could be done if there were some agreement as to what constitutes a recurrence and if someone would tell us how long after operation patients are out of danger of recurrence Do symptoms of ulcer with a negative roentgenogram constitute a recurrent ulcer? Does a suggestive roentgenogram without symptoms of ulcer justify such a diagnosis? Does a single postoperative hemorrhage mean that the patient has a recurrence? We really have no way of telling the exact frequency of recurrent ulcer because of these factors and also because of the time element, these recurrences may appear many years after successful operation for ulcer, as in one of the cases to follow

The questionnaire method of evaluating postoperative results has been criticized, but frequently it is the only one available Another thing to be considered is the difficulty of roentgenologic diagnosis We are willing to accept the competent roentgenologist's report as final, but there is a high percentage of error in average roentgenologic reports on previously operated stomachs Interpreting roentgenographic and

roentgenoscopic findings is largely a matter of experience, one has to see a great many such cases to be sure of the ground

How soon do recurrent ulcers form? Probably most of them form very soon after operation, some wit has said that they begin to form if they form at all, while the skin is being sutured One patient whom we saw some years ago had postoperative pulmonary complications and a ventral hernia developed, when the abdomen was opened a few weeks later, to close the hernia a large ulcer at the gastro-enteric stoma was visible. There had been no symptoms whatever Another patient underwent gastro-enterostomy, but the stoma never functioned satisfactorily, because of gastric retention, the patient was operated on again, and the surgeon found extensive gastrojejunitis involving the stoma It has been shown that most of the recurrent ulcers are giving symptoms within eighteen months after the primary operation They probably begin as localized superficial lesions which eventually become extensive ulcers There is a marked tendency to penetration localized infiltration, and formation of inflammatory peri anastomotic and periduodenal masses, and there is a decided tendency to bleeding although the original ulcer may have caused no such symptoms On the average, recurrent ulcers are more troublesome than those originally formed but this is not always the case such ulcers may produce very few symptoms That unfortunately appears to be the gamble one takes in advising gastric operations on peptic ulcer

Before returning to discussion of our cases, I would like to call attention to the following points in the history of recurrent and reactivated ulcers (1) Symptoms are generally irregular (2) Periodicity and relief from taking of food and alkali frequently are lacking. (3) Control under medical treatment is difficult (4) There is a shift in the site of pain The patient may originally have had pain in the epigastrium or just to the right of it the pain of the recurring ulcer is at an entirely different point, whereas in reactivation of old ulcers the change in the site of pain is less striking (5) The tendency to hemorrhage of patients who had not previously bled

is very striking (6) Unusual mechanical and motor phenomena, such as evidence of physiologic block and heightened gastro-intestinal irritability, are very common These phenomena may be attributable to local foci of inflammation in the wall of the bowel (7) There may be local signs of peritoneal irritation and occasionally the formation of palpable tumor masses at the site of anastomosis

The first case we wish to present is that of a patient who came to the clinic originally with duodenal ulcer, complicated by marked nervous instability and a background of addiction to alcohol

Case I.—The patient, a lawyer, aged forty-five years, registered at the clinic February 23, 1934, with a presenting complaint of dyspepsia of twelve years' duration He gave a history of having had, previously, a single severe attack of pain in the upper portion of the abdomen, which had come on shortly after eating and which had been relieved by a hypodermic injection of morphine sulphate While he was in the army in 1918 he had begun to drink rather heavily and had continued to be a periodic drinker until October, 1933, when his indigestion had put a stop to the practice In 1922 indigestion had begun as a mild gnawing, epigastric distress, occurring two to three hours after meals, and relieved by taking of food and soda This distress had appeared after every meal for a week or more at a time, it had recurred periodically and definitely had been made worse by drinking bouts In 1923 roentgenologic examination of the stomach had given negative results, but the patient had been advised to take alkaline powders, which he did with temporary relief Thereafter, there had been occasional flare-ups of symptoms until October, 1933, when they had become much more marked At that time the gnawing epigastric distress had begun about an hour after meals and also had awakened the patient at 1 or 2 a m , taking of food and alkalies, however, had continued to give relief There had been no vomiting or melena, and the bowels had been regular in action In February, 1934, the distress had shifted to a point 2 to 3 inches (5 to 7 6 cm) to the right of the mid epigastrium, there had not been any extension of the pain, except for occasional, stabbing discomfort in the thorax On roentgenologic examination made at home, December, 1933, diagnosis of gastric ulcer had been made, typical duodenal deformity, presumably attributable to duodenal ulcer, also had been noted The question of disease of the gallbladder also had been raised

Physical examination at the clinic revealed a "high-tension," nervous individual, well nourished but apparently having considerable epigastric distress The epigastrium was tender, grade 1, and there were small, external hemorrhoids Otherwise examination gave negative results Analysis of gastric content following an Ewald test meal disclosed total acidity of 120 units and free hydrochloric acid of 114 units (Töpfer's method) The content obtained

measured 80 c.c. On roentgenologic examination of the stomach and duodenum a duodenal ulcer was found. A roentgenogram of the gallbladder showed it to be functioning poorly.

The patient was hospitalized and a medical regimen for ulcer was ordered. Gastric acids were tested after stimulation by histamine. Total acidity was 148 and free hydrochloric acid 136. The gastric content obtained measured 40 c.c. After eighteen days of treatment the man was dismissed March 14, 1934. He was given a diet suitable for an ambulatory patient with ulcer and was ordered to take milk between meals three times daily, mucin daily before meals and alkaline powders an hour after eating.

On April 7, 1934 the patient returned to the clinic saying that he was definitely worse. He complained of moderate pain, much gas, borborygmus and martinal discomfort in the right upper quadrant of the abdomen. The distress was increased quantitatively by an increase in the diet.

April 9, 1934 gastroduodenostomy and cholecystectomy were performed by Dr. Judd for chronic duodenal ulcer and chronic catarrhal cholecystitis with adenomyoma. A diagnosis of hepatitis, grade 3, was made at the time of operation. The patient made an uneventful convalescence until a week after operation when he began to complain of considerable epigastric pain which occurred at night and was relieved by taking soda. April 24, 725 c.c. of watery content was recovered on aspiration of the stomach; the total acidity of this was 100 units and the free hydrochloric acid 68 units. On repeated gastric aspiration retention diminished rapidly and the patient was dismissed to follow a diet suitable for an ambulatory patient with ulcer.

The patient returned to the clinic August 1934 for reexamination at which time he complained of occasional mild epigastric distress. He stated that he felt better when he took three or four alkaline powders daily. Roentgenologic examination revealed evidence of the former lateral gastroduodenostomy; the stoma was functioning normally. There was no evidence of ulcer.

The patient returned to the clinic January 2, 1935 and stated that he had never been entirely comfortable since operation. He had had very little pain even when the stomach was empty, but he complained of much bubbling and gurgling after meals and some fullness and distress in the epigastrium which occurred about 4 or 5 p.m. daily. He had closed his law office and had devoted his time to keeping an elaborate chronologic account of all his digestive complaint.

Examination revealed an apprehensive individual with definite hypochondriacal tendencies. The total acidity of the 10 c.c. of content obtained was 82 and the free hydrochloric acid 24 units. A roentgenogram of the stomach again gave evidence of former lateral gastroduodenostomy and of a freely functioning stoma. Again no ulcer was noted and the patient was advised to return to work.

The patient returned again February 5. At this time he complained of [illegible] flatulence and passage of much gas by rectum. He was depressed and there was a continual feeling of fullness which was worse in the morning. Shortly before there had been some pain at the umbilical margin to the right and with some extension to the back. Distress had been relieved by taking [illegible] although the patient was [illegible]

[illegible]

a short time after a meal He had been losing weight and strength, and there was a moderately tender area to the right of the epigastrium On roentgenologic examination, evidence of the former gastroduodenostomy was obtained, as before, and a recurrent duodenal ulcer was present, a definite ulcer crater could be demonstrated

Dr Kirklin This is a patient in whom I was very much interested because I was trying to get some data on the roentgenologic appearance after lateral gastroduodenostomy This is an operation in which the duodenum and the stomach are anastomosed just proximal to the pylorus You can appreciate that this makes a marked angulation and would produce a considerable amount of change in form from a roentgenologic standpoint At the time, we were studying the stomach which had been subjected to operation, and since we did not have any late postoperative roentgenograms after lateral gastroduodenostomy, I wrote to this patient and asked him to return for reexamination We had examined him shortly after operation, and as is expected at that stage, the anastomosis was not as yet functioning very well There was considerable secretion and marked atony of the stomach, conditions which are found almost routinely within a month or so after operation (Fig 42, *a*) The man returned in August (Fig 42, *b*), and I wonder now how much my request had to do with his increasing apprehension about himself

I cannot show the evidence of an ulcer crater in his most recent films, but you can see the marked deformity at the pylorus The only reliable roentgenologic evidence of ulcer in these cases is demonstration of the ulcer crater itself Roentgenograms were negative so far as any recurrence was concerned, until the last examination, February 25 At that time, Dr Camp found a definite ulcer crater These roentgenograms will show much more clearly the way these stomachs appear to us At the left is a roentgenogram made within two or three weeks from the time the lateral gastroduodenostomy was performed The stomach is atonic, and very little barium is going through the pylorus, hardly enough to allow the change in form to be visualized On the right is a roentgenogram

taken two months after operation The stomach has regained its tonus, and the edema and reaction around the anastomosis

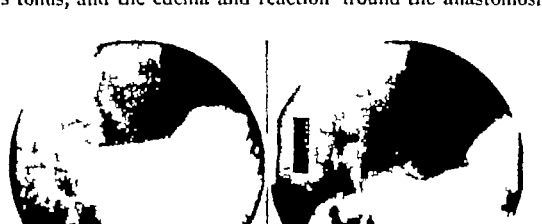

Fig 4 —a Roentgenogram made three weeks following operation showing usual atony of tomach *b* roentgenogram made four months later showing typical deformity produced by lateral gastroduodenostomy with normal function

have subsided Now we have a true picture of a stoma that is functioning normally after lateral gastroduodenostomy The

Fig 43 —a Deformity of the duodenum caused by a chronic duodenal ulcer *b* same case after knife excision of ulcer and resection of the pylorus

stomach is of normal size and tonus On the left is a roentgenogram giving evidence of the deformity produced by a duodenal ulcer (Fig 43 *a*) Pyloroplasty was performed, the

ulcer was excised, and the incision was closed in the opposite direction from that in which it was made Some time later the patient had symptoms suggesting a recurring ulcer The persisting deformity is shown in Fig 43, *b*

Dr Snell I think that Dr Kirklin has said most of the really important things about this patient and about the surgical procedure in question

There are two things I might mention After operation, this patient had nocturnal pain and gastric retention I think those are two symptoms that can never be overlooked Later, he had pain from a point just to the right of the epigastrium, around the ribs to the back It was not severe, but under these circumstances it was almost pathognomonic of ulcer The patient's obvious neurotic tendencies, however, confused the picture

Lateral gastroduodenostomy was first suggested by Jaboulay, and has been endorsed by Wilkie Their results have been, in general, quite satisfactory As to the advantages of the operation, it is fairly easy to secure wide anastomosis, which allows for good drainage of the stomach, the gastric juice is diverted into the duodenum, which is the most acid-resistant portion of the bowel A disadvantage that has been noted is that the anastomosis sometimes functions poorly immediately after operation The mechanical difficulties do not occur often and as a rule they eventually clear up with a minimal amount of trouble However, until the stomach has resumed its tonus, the gastric juices accumulate in the stomach, and that of itself may favor recurrence Also the acid "stream" strikes the angulated bend of the duodenum and may affect the mucosa at that point

The practical lessons in this case are important Rivers and Eusterman have pointed out that we should never minimize the complaints of a patient who has undergone an operation for ulcer This man brought with him a voluminously written history, in which he had recorded every intestinal gurgle down to the minute, he had listed the fluid and food he had taken, and their immediate and remote effects Be-

cause of the little scrap of paper" I had put him down as a neurotic individual But he came back with evidence of ulcer and a crater was found When patients do return with postoperative complaints, they should be kept under observation and should be examined and reexamined Another important thing in this case was the terrifically high gastric acidity after histamine had been used as a stimulus, free acidity was 136, and total 148, we were collecting almost 400 c c of gastric content in two hours Obviously, reoperation may be necessary in this case, and if it becomes necessary radical resection is probably the procedure of choice *

Case II.—The patient a man aged thirty nine years registered at the clinic in December 1929 at which time he complained of indigestion which had troubled him during the preceding year He described a burning gnawing epigastric pain which came on about three hours after meals and which awakened him regularly about midnight Temporary relief was obtained from taking food milk soda and "Pfunder's tablets." The symptoms had disappeared spontaneously after one month and had returned two months before his admission to the clinic

Physical examination gave essentially negative results Roentgenoscopic examination of the stomach was negative on two occasion After an Ewald test meal 300 c c of gastric content were obtained of which total acidity was 84 and free hydrochloric acid 2 The man returned home to follow an ulcer regimen for ambulatory patients and was comfortable until the following autumn

He returned in November 1930 at which time roentgenologic examination revealed a duodenal ulcer with a large crater the latter feature had not been noted before He was subjected to operation on November 8 by Dr Dixon A small ulcer was found on the posterior wall of the duodenum The ulcer the cap of the duodenum and the anterior wall of the pyloric sphincter muscle were excised and the resulting incision was closed as after gastroduodenostomy The gallbladder was normal The upper his gave evidence of chronic inflammation and was removed Postoperative convalescence was uneventful The man returned home and on ambulatory ulcer patient to follow a suitable regimen and was well for several month Later he noted that a few be adhered strictly to his diet he was comfortable but that any laxity in diet would promptly lead to epigastric distress similar to that which he had had before operation

The patient returned in September 1931 for roentgenological examination At which time an Ewald test meal revealed total acidity of 92 free acidity

* Re examination in April 1932 showed that the crater had disappeared roentgenologically and the patient was symptom free There were no further symptoms present and except for the occasional belching of gaseous material noted by himself and others

86 Roentgenologic examination revealed a duodenum changed in form by previous operation and a small pouch, or crater, near the center of the duodenal cap The man was reëxamined after six weeks of strict management for ulcer, and no evidence of a crater was seen in the duodenum

The man returned again in March, 1933, having had numerous short episodes of distress, which were becoming more persistent and constant There had been much pain at night during the six weeks before his return Roentgenologic examination revealed a recurrent duodenal ulcer He was sent to the hospital but was unable to remain there more than a few days, because of pressing business obligations It was explained to him, on dismissal, that it was absolutely necessary for him to secure more recreation, relaxation, and rest, and to avoid many of the nervous strains to which he had been subjecting himself, if he was to avoid further surgical treatment

The patient returned in November He had had numerous flare ups of the same distress but said that as long as he did not work he felt fairly well Any attempt to carry on his work would cause return of his trouble To avoid further operation, if possible, he was sent home Minor changes were made in his treatment and he was dismissed to continue on medical management

He returned again, in January, 1935, complaining of having had numerous episodes of severe epigastric distress, with flatulence and fullness The pain had definitely shifted to the right, and extended along the margin of the ribs on the right

Because of the severity and persistence of the symptoms, operation was performed February 19, 1935, by Dr Walters, who found a large, perforating duodenal ulcer involving a portion of duodenum about 5 cm in diameter, perforating into the falciform ligament of the liver adjacent to the gallbladder, and involving the wall of the latter organ The area of inflammation in the duodenum was so marked that gastric resection could have been performed only at the greatest risk The area of inflammation was inverted with a purse string suture and was covered with omentum, posterior gastro-enterostomy was performed

Dr Kirklin Here, again, we have an operation that changes the form of the pylorus and outlet of the stomach As is generally known, any constant deformity of a duodenum which has not been operated on can safely be interpreted as evidence of duodenal ulcer, but this finding does not mean that the ulcer is active or productive of symptoms The deformity may be only the scar of a previous ulcer or it may be associated with spasm If a crater is definitely visualized, we are certain we are dealing with an active ulcer In dealing with a patient whose duodenum has been operated on, then, we cannot rely on the mere presence of deformity of the duodenum in diagnosing an ulcer We must see the ulcer crater before we can

make a diagnosis of recurring ulcer In this case as in the previous type of case in which operation had been performed, we were able to demonstrate the presence of an ulcer crater, the shadow of which can be seen on the film (Fig 44) The crater was also seen fluoroscopically, and there was evidence of spasm The deformity was more marked than we would expect to see following pyloroplasty only, and we concluded

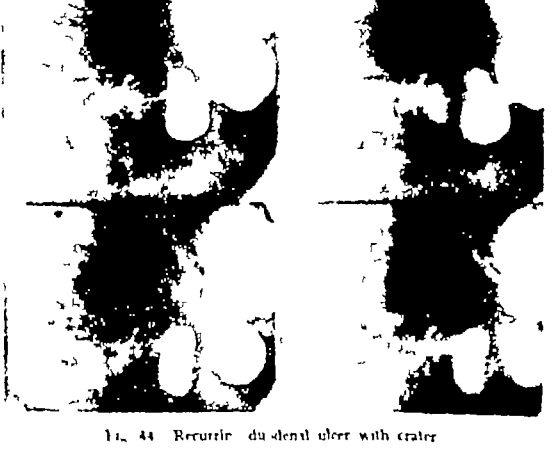

Fig. 44 Recurrent duodenal ulcer with crater

that a large part of the deformity was attributable to duodenitis associated with the ulcer

The result of the first examination in this case represents a rather interesting group of cases from the standpoint of roentgenology when this patient first came to the clinic there were two negative roentgenologic examinations of the stomach, but I find on the fluoroscopic notes that the roentgenologist who examined the patient commented on the fact that there was an anatomic deformity distal to the duodenal bulb The

same note was made on the second examination a few days later When the patient returned one year later we found a large crater near where the deformity was noted at first examination, just distal to the first portion of the duodenum Sometimes these deformities far out in the duodenum are very *confusing*

Dr Snell The only comment I want to make about this case is that in March, 1933, a crater had not formed and the extraduodenal inflammatory process had not developed Later this man had attacks of severe, excruciating pain, which extended to the back, along the right costal margin, and, because of these symptoms we predicted that an inflammatory and penetrating ulcer would be found Dr Walters found such an ulcer which, as has been said, had penetrated into the falciform ligament of the liver adjacent to the gallbladder The inflammation in the duodenum was so marked that the contemplated gastric resection was impossible Extensive resection could possibly have been done at an earlier date, with low risk and good assurance of success

From the surgical standpoint, pyloroplasty is particularly applicable in the treatment of early duodenal ulcer and has given consistently good results The mortality is low, and the end results compare favorably with those of gastro-*enterostomy Recurrences are not as serious as with* gastro-enterostomy, there is an opportunity for radical operation, if it is needed Pyloroplasty has another good surgical feature, if another ulcer forms, it is possible to perform gastro-enterostomy Although excision of the lesion would have been a more acceptable operation, the gastro-enterostomy which was performed may end the trouble The high values for gastric acids are again a factor in this case, pyloroplasty does little to reduce acidity I would like to emphasize the shift of the pain in this patient's case, and also the fact that the crater disappeared when the patient was under medical management

I would like to ask you, Dr Kirklin, how seriously you take this disappearance of the crater?

Dr Kirklin We take it very seriously because you clin-

icians have told us that the symptoms often disappear with disappearance of the crater

Dr Snell (continuing) We are, of course, entitled to speculate on the outcome of gastro-enterostomy in this case The patient had had a recurrence of ulcer after pyloroplasty, will he have one after gastro-enterostomy? He may get along fairly well, but the ulcer forming patient always presents a problem We hope the progress of this patient will exceed our expectations

We want to turn next to the subject of recurrence of ulcer following gastro-enterostomy In former years this operation was expanded to cover the whole known range of gastric pathologic conditions, but now we know that it has some definite limitations It still gives the best results of any single operative procedure in the hands of surgeons all over this country, it is in good standing in England and in Canada, although under some suspicion on the Continent.

Case III —The patient a man aged seventy-one year first registered at the clinic in 1921 He had had indigestion for three years before admission and a few months before registration he had gastric hemorrhage and melena Dr W J Mayo excised with the cautery a bleeding and perforating duodenal ulcer which was causing actual obstruction Posterior gastroenterostomy also was performed and the appendix removed The man was entirely well for ten years after this operation In 1931 he began having attacks of upper abdominal distention and vomiting which were progressively more frequent and severe Melena was noted on several occasions He returned in the autumn of 1933 feeling miserable and having lost 15 pounds (6 8 kg)

Dr Walters disconnected the gastro-enterostomy anastomosis and performed knife excision of a gastrojejunal ulcer the crater of which was cm in diameter and which was perforating into the transverse mesocolon The duodenum was found to be contracted at the site of the old duodenal ulcer Since the patient was seventy-one years of age gastric resection did not seem advisable and the duodenum had been shortened so that satisfactory pyloroplasty could not be performed For these reasons anterior gastro-enterostomy with enteroanastomosis was performed

The patient was well for about six months when attacks of sharp pain returned These pains seemed to start at the margin of the ribs in the left anterior axillary line and to extend forward to the midline on the left The pain was worse three or four hours after meals and was relieved by taking effervescent powders There was no vomiting The pain increased in frequency and severity there was some loss of weight but no hematemesis or melena

The patient was examined in August, 1934, and a large jejunal ulcer, 2 5 cm in diameter, just distal to the stoma, was visualized by roentgenologic examination Fractional analysis of gastric content after a test meal disclosed free hydrochloric acid ranging from 16 to 66 units, and total acidity of 60 to 84 units The symptoms were completely relieved following ten days in hospital on strict management for ulcer The man returned in October and December, 1934, for further examination Evidence of a large gastrojejunal ulcer, with an accessory pocket extending downward from the stoma, was found by roentgenologic examination The patient returned again January 31, 1935, for another examination He had been on a very strict regimen at home but still had not been entirely comfortable, particularly at night. Brief periods of comfort alternated with periods of mild distress Under strict management in hospital the symptoms usually subsided, only to recur sooner or later at home

Dr Kirklin Let us look at the roentgenograms in the case Here is the first roentgenogram, taken after the second operation, the anterior gastro-enterostomy This roentgenogram was made in August, 1934 and the patient was operated on in November, 1933 The shadow of the large crater can be seen The fact that the stomach contained only a small amount of barium, allows study of the gastric mucosa at and near the stoma The crater of the ulcer appears as a "blob" of barium, it is large, much larger than we usually see following posterior gastrojejunostomy The next roentgenogram was taken in December, 1934, and the shadow of the large crater still can be seen There also appeared to be a great deal of local edema, much more than there was at the previous operation, resulting in distortion of the mucosal pattern at the stoma The large, white shadow is that of the crater with the accessory pocket (Fig 45, *a* and *b*) It has been our observation, and this is confirmed by Dr Balfour, that gastrojejunal ulcer, following anterior gastro-enterostomy, is not infrequently symptomless until the ulcer is of an appalling size When it is discovered, it is difficult to conceive that the patient had not had more symptoms

Because of the altered physiologic and anatomic characteristics of the viscus, study of the stomach after operation is the most difficult field of gastro-intestinal roentgenology This roentgenogram, made in another case, represents a fairly

normal result following gastrojejunostomy (Fig 46, *a*) Notice how the mucosal pattern of the jejunum blends with the pattern of the stomach We observe this during fluoroscopic examination, by manipulating the walls of the stomach Notice the site of the anastomosis in this, still another case, there is marked deformity Instead of the normal mucosal pattern appearing, it is greatly altered and there is considerable narrowing of the jejunum, which is probably attributable to jejunitis There is very definitely the crater of an ulcer at the margin of the stoma (Fig 46, *b*) We usually find these ulcers just distal to the anastomosis

a *b*

Fig 45—*a* Large jejunal ulcer with accessory pocket just distal to the stoma Film made with pressure *b* same case as that represented in *a* film made without pressure

The next roentgenogram (Fig 46 *c*) was made in another case of jejunal ulcer following gastrojejunostomy the shadow of the ulcer can be seen in the distal limb of the jejunum There is a deformity of the gastric rugæ at the stoma resulting from inflammation Notice also, the deformity which still remains in the duodenum from the old scar of the ulcer The patient is a physician, a former fellow of The Mayo Foundation

The next roentgenogram represents a jejunal ulcer with a large crater This also followed anterior gastro-entero-stomy and the patient had very few symptoms until shortly before

the examination in the course of which this roentgenogram was made The roentgenogram on the right was taken just a few minutes later, after filling of the stomach with barium It

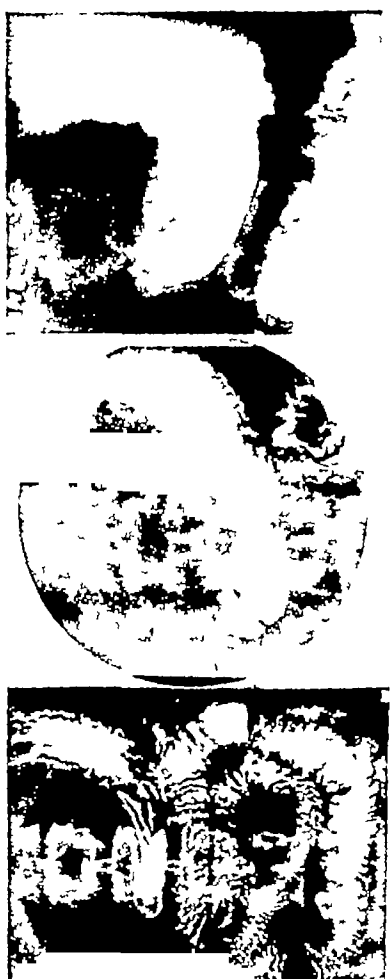

Fig 46—a, Normal function after gastrojejunostomy Note the normal mucosal pattern of the stomach and jejunum, *b*, imperfect function after gastrojejunostomy with ulcer crater on distal limb of the jejunum, *c*, gastrojejunostomy with stiffening of the jejunal wall just distal to the stoma This is a secondary sign of gastrojejunal ulcer or jejunitis

emphasizes the importance of examining these patients with only a small amount of barium in the stomach That is one of the reasons why it is important to know that the patient has had a previous gastric operation Otherwise, if the patient is

allowed to drink the entire mug of barium the lesion or the anastomosis may be covered up

So far we have discussed the direct signs of gastrojejunal ulcer I might say that the surest evidence of jejunal ulcer or of gastrojejunal ulcer is the visualization of the crater The most reliable secondary sign is the evidence of spasticity produced by the jejunitis Here is such a case Notice the evidence of spasticity the valvulæ conniventes of the jejunum do not blend with the rugæ of the stomach This constitutes only suggestive evidence of jejunal ulcer In the absence of a crater we might say there is some indirect evidence of ulcer, but it is not definite

Dr Snell I should like to say just one word about the most characteristic single symptom of gastrojejunal ulcer, and that is the shift of the pain Ordinarily, in duodenal ulcer the pain is midepigastric, under the third button of the vest. When a gastrojejunal ulcer forms, the pain shifts to the lower part of the abdomen If you ask such a patient to indicate the direction of extension of the pain frequently he will point downward to the testes or to the groin If the patient has that type of extension of pain, we can be reasonably sure he has a gastrojejunal lesion, whether or not the lesion is visualized roentgenologically

Gastro-enterostomy gives surprisingly good results, considering the fact that in the absence of pyloric obstruction it does not seem physiologically quite sound because the operation allows the gastric juice to enter the portion of bowel where resistance to the digesting action of gastric juice is poor In this case, the symptoms for which the patient registered in 1933 were not those of ulcer but those of obstruction He had no great amount of pain but rather difficulty in emptying the stomach Gastrojejunal lesions after anterior gastro-enterostomy as Dr Kirklin has emphasized are usually extraordinarily severe and are well along in their course before we see the patients, in a great many cases there are associated abdominal masses When you see a patient who has an ulcer an abdominal scar, and an abdominal mass in

neath the scar, you at once can think seriously of a previous anterior gastro-enterostomy I don't know why a man of seventy-one suddenly started to be an ulcer-former Usually the older a man gets, the lower is the gastric acidity and the less probability there is of recurrence of ulcer

I do not want to give the impression that many patients who undergo gastro-enterostomy have subsequent gastro-jejunal ulcer, and that many types of pyloroplasty turn out badly Neither are we without recourse when these patients come to us, since radical resection nearly always is possible The number of ulcers that form after resection, even in so-called ulcer-formers, is small Dr Weir reviewed a large series of cases, and his article should be consulted for details I think more radical resections have been done lately at the clinic, with the idea of maximal reduction of gastric acidity We do not know exactly why gastric resection will abolish or greatly reduce gastric acidity, it is not because we remove the acid-secreting cells, neither is it entirely attributable to the size of the anastomosis The Germans say a hormone is secreted by the pyloric antrum, that stimulates the acid cells to secrete Priestley and Mann, in their experiments, have not substantiated this observation

Question Have you any idea which patient is going to be an "ulcer-former"?

Dr Snell If we did have such foreknowledge we would advise gastric resection to begin with The last two patients whose cases we have reported were quiet, restrained, hard working people, and there was nothing to suggest the nervous temperament of habitual ulcer-formers We have no way of knowing positively which patients are in danger of having recurrent ulcers, but we are inclined to anticipate them if patients are of the high-strung, aggressive type, particularly if a large volume of highly concentrated gastric juice also is present.

Case IV —A salesman, aged forty-seven years, registered at the clinic in July, 1928, complaining of periodic dyspepsia of nearly thirty years' duration His distress was characterized by severe, burning, epigastric pain, which came

on an hour and a half to two hours after meals and which was relieved by the taking of food and soda Coarse foods and minor dietary indiscretions increased the distress There were no remarkable physical findings and examination of the blood and urine disclosed nothing of consequence Analysis of gastric content after an Ewald test meal revealed free acidity of 62 units and total acidity of 74 units Fluoroscopic examination of the stomach gave evidence of a duodenal ulcer Because of the severity of the distress and the long history surgical treatment was recommended An encircling ulcer was found just below the pylorus with definite scarring of the anterior and posterior walls of the duodenum the stomach was somewhat dilated but a gastric ulcer could not be demonstrated Posterior gastro-enterostomy was performed and the patient made an uninterrupted recovery

He was perfectly well until the summer of 1933 when a mild epigastric distress developed together with a "sticking" pain which extended upward into the left side of the chest Both complaints were aggravated by dietary indiscretions These pains became gradually worse and the man returned to the clinic in November 1933 to see if any cause for them could be determined On inquiry it was noted that there was no constant relationship in time between the taking of food and the pain and that ease from the taking of food was inconstant Physical examination again gave essentially negative results. There was no anemia and the patient was in good general condition. Analysis of gastric content after the test meal disclosed free hydrochloric acid of 3 and total acidity of 38 Roentgenologic examination of the stomach disclosed that the gastro enteric stoma was free that the pylorus was patent and also that there was a large ulcerating lesion on the lesser curvature of the stomach at the level of the incisura It was decided that the lesion was probably a benign ulcer and in order to give the patient an opportunity to try medical management he was hospitalized Symptomatic relief was almost immediately obtained and repeated examination of the stools did not disclose blood Within two weeks the patient was so comfortable that he was allowed to leave the hospital Repeated examinations of the stomach were made with results which Dr Kirklin will present The lesion gradually decreased in size The patient has remained perfectly well in spite of the strenuous manner of his life the only residue of the previous ulcer at present is a very small irregularity of the incisura

Dr Kirklin This series of films shows very well the process of healing of gastric ulcer The original lesion was large and penetrating (Fig 47 *a*) but there was nothing about it to suggest a meniscus type of ulcer crater such as is often associated with early carcinomatous ulceration These films were taken after the patient had been under treatment for about two weeks (Fig 47 *b*) The lesion is very much smaller and appears to be contracted inward at the base In the last films the only visible defect is so minute that it could not be seen

on fluoroscopic examination, in the films, however, there is a tiny irregularity which probably is attributable to puckering of the mucosa at the point once occupied by the crater (Fig 47, *c* and *d*) From a roentgenologic standpoint I feel certain

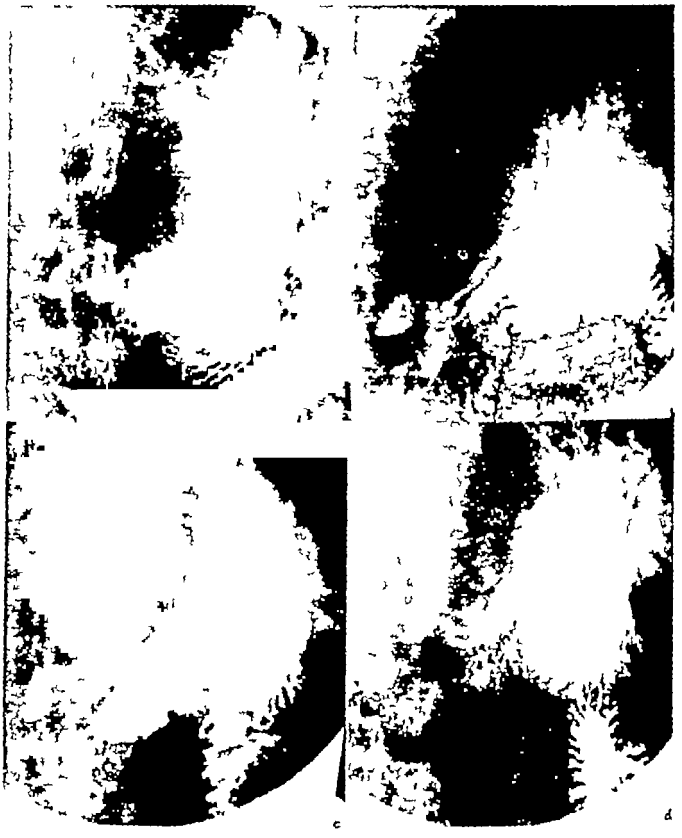

Fig 47.—*a*, *b*, *c*, *d*, Showing a freely functioning gastro-enterostomy and a perforating ulcer on the lesser curvature at the angle of the stomach Regression of the ulcer during treatment

that the patient has had a benign lesion and that it has completely healed

Dr Snell While gastric and duodenal ulcers are not infrequently associated, it is very unusual to find gastric ulcer after a successful gastro-enterostomy for duodenal ulcer One

sees an occasional patient with gastritis, with or without ulceration, when the gastro-enteric stoma becomes obstructed, but solitary gastric ulcers are rarely found under the same conditions The large size of the lesion in this case raised the question of malignancy, and we were at one time tempted to advise re-operation However, the patient was very anxious to try medical treatment and the results obtained were so good that we can properly congratulate him and ourselves for pursuing this course As a rule, benign gastric ulcers heal rapidly under medical management. The difficulty is to be certain that these lesions are not carcinomas None of the ordinary criteria serve to distinguish the two conditions with absolute certainty, and we rarely attempt medical treatment unless the patient is willing to return for repeated roentgenologic examinations and gastroscopy, if the latter seems indicated It is unfortunate that recurrent or anastomotic duodenal ulcers do not heal as readily as do these gastric lesions I imagine that this patient's progress has been facilitated by the presence of a normally functioning gastro-enteric stoma, which has served to keep his gastric acidity low and to make its control an easy matter

There is one point in the patient's history which should be mentioned the gastric ulcer produced an entirely different type of pain from that which he had noted before gastro-enterostomy It was irregular in appearance, not particularly severe, and extended toward the thorax This type of distress is commonly noted when benign gastric ulcers develop at this level

Case V.—The patient a man aged thirty five years registered at the clinic May 1 1928 His chief complaint was of "stomach trouble" which he had had since the autumn of 19 and which consisted of burning pain in the epigastrium which would come on two hours after eating and at about [illegible] It could always be completely relieved by taking of food or soda. The one exception to the pain had appeared for several months after two weeks of treatment with diet rest and alkalies post hoc Since that time however the man had had recurrences of the same type of distress lasting from one to four weeks and occurring at intervals of from three to twelve months He was [illegible] stomach trouble [illegible] pain [illegible] of penetration

[illegible]

Physical examination gave essentially negative results except that a small colloid goiter was found The concentration of hemoglobin was 75 per cent. Analysis of gastric content following an Ewald test meal revealed total acidity of 104 units and free hydrochloric acid of 84 units, the content recovered measured 50 c.c Roentgenologic examination revealed duodenal ulcer May 10, Dr Balfour excised a duodenal ulcer, performed pyloroplasty, and removed the appendix The patient made an uneventful recovery

The man returned to the clinic November 27, 1928 He stated that he had begun to have more epigastric distress very soon after his dismissal in May The pain was similar to that which had occurred before operation, but there was also an added feature namely, extension of the pain to the back. This type of pain occurred about 2 or 3 p.m and was relieved by the usual measures

Physical examination revealed tenderness, grade 1, in the right upper quadrant of the abdomen Total gastric acidity was 64 and free hydrochloric acid 42 Gastric content aspirated measured 60 c c The concentration of hemoglobin was 61 per cent The roentgenologist reported that the duodenum was deformed by operation No crater was seen It was felt, nevertheless, that the man had a recurrent duodenal ulcer, and he was hospitalized for eighteen days under strict management for ulcer Tonsillectomy was performed December 10 He was dismissed from the hospital December 17, feeling much better

The third registration was on November 30, 1931 The patient stated that the longest period of relief from symptoms of ulcer since his previous visit had been one month The symptoms had gradually become more pronounced, and the pain more constant, and more likely to awaken him at night He had had several tarry stools in this interval, but nothing to suggest large loss of blood At this time, total acidity of gastric content was 60 and free hydrochloric acid 48 The gastric content obtained measured 200 c c Roentgenologic examination of the stomach revealed that the cap was deformed by previous pyloroplasty, still no crater could be visualized A strict regimen for ulcer gave partial relief of symptoms, but in spite of prolonged absence from work, removal of foci of infection, and careful dieting, the symptoms recurred with increasing frequency and severity Finally, in April, 1931, partial gastrectomy and partial duodenectomy, with a Polya anastomosis was performed by Dr Balfour for multiple, subacute, perforating duodenal ulcers The man made a good recovery from operation, and was dismissed May 23, feeling comfortable. We saw him the following August, he was much improved except for a slight feeling of nausea after taking liquids

Analysis of gastric content revealed achlorhydria, the highest total acidity was 12 units Roentgenologic examination revealed that the stomach was in good condition and that the anastomosis was free

The patient returned December 18, complaining of pain in the left arm, which apparently was attributable to ulnar neuritis As far as his stomach was concerned, he had been fairly comfortable except for slight nausea in the morning The patient remained in Rochester nearly all of 1934 We subsequently learned that he had domestic and financial difficulties and that he had been working steadily In spite of these factors, his digestion was good, there was no return of gastric acidity, and repeated roentgenologic examinations of the stomach gave negative results

Dr Kirklin This is the film made about a month following the resection (Fig 48) You can see that the stomach is somewhat lacking in tonus, which is not surprising so soon after operation A second roentgenogram, taken several months later, disclosed that the stomach had regained its tonus and was emptying normally Notice, on this film, the normal mucosal markings at the site of the anastomosis Here is his stomach later, the anastomosis was functioning normally In examining the stomach postoperatively it is necessary that the roentgenologist know something of the type of operation

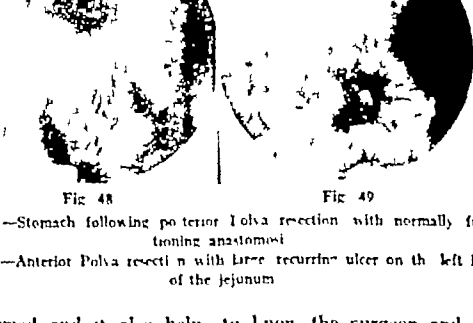

Fig 48 Fig 49

Fig 48—Stomach following posterior Polya resection with normally functioning anastomosi

Fig 49—Anterior Polya resection with large recurring ulcer on the left limb of the jejunum

performed and it also helps to know the surgeon and the technic which he employs The roentgenologist thus can be guided as to any peculiar appearance of the stomach because he finds very few surgeons even in the same institution, who do exactly the same type of operation

This film is taken from one of the few cases in which we have seen a recurring jejunal ulcer following Polya resection (Fig 49) The most satisfactory immediate mechanical results from our standpoint are those which we are following the Polya operation

Dr Snell I would like to close the discussion with the

statement that recurrences are not necessarily hopeless but can be satisfactorily treated by skillful operation and good postoperative care The last patient described has had every conceivable psychic and occupational handicap and yet he has remained free from symptoms I have records of a number of cases in which gastric, gastrojejunal and recurrent or reactivated duodenal ulcers, appearing after primary operations for duodenal ulcer, have healed under medical management At least there is no demonstrable lesion on roentgenologic examination, the patients are symptom-free, and are pursuing their usual occupations Surgical treatment is necessary in the majority of cases, and if the recurrent lesion is not such as to hamper the surgeon in the performance of partial resection, good results are the rule If we could solve the riddle of why ulcers form, a more satisfactory therapeutic approach would be possible

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CLINICAL MANIFESTATIONS OF TRACHEAL AND BRONCHIAL OBSTRUCTION WITH CERTAIN BRONCHOSCOPIC OBSERVATIONS

PORTER P. VINSON

The subject I want to discuss today is one that I approach with trepidation and in a spirit of questioning rather than with a desire to tell you what I may or may not know about it. I wish to discuss the clinical manifestations of tracheal and bronchial obstruction, and to give some bronchoscopic observations, along with summaries of cases.

In dealing with tracheal and bronchial obstruction, the question of asthma must always be considered in diagnosis, for at some time or other the diagnosis of asthma has been made in almost all cases in which patients have suffered from obstructive lesions of the respiratory tract, particularly if the obstruction has been associated with stridor. It is interesting to note that in certain types of asthmatic bronchitis, clinical evidence of localized bronchial obstruction is frequently observed. When this localized obstruction persists, bronchoscopic examination is required to determine whether or not an organic obstruction is present.

A patient whom I saw a few days ago had suffered with chronic asthmatic bronchitis for a number of years. His symptoms were increased on exercise and after exposure to dust, but were not present at night, and he had not had any paroxysmal attacks of dyspnea. Examination of the thorax revealed complete obstruction of breath sounds to the upper lobe of the left lung. A case of that type would have required bronchoscopic examination if the physical findings had persisted. However, repeated observations disclosed the fact

that other bronchi seemed obstructed at subsequent examinations, and the fluctuating character of the physical signs made bronchoscopic study unnecessary

In cases in which there is evidence of localized obstruction, but a neoplasm or actual bronchial stricture does not exist, bronchoscopic examination rarely reveals the cause of the signs that are elicited on physical examination Occasionally, a thick, tenacious secretion is observed, but after this has been aspirated, the same physical signs are likely to persist On bronchoscopic examination, I have not been able to detect in the bronchi changes that suggest bronchial spasm An interesting point in bronchoscopic examination of patients who have asthma or asthmatic bronchitis is that the symptoms may be relieved by the examination and that this relief may persist for indefinite periods One is probably justified in carrying out bronchoscopic examination in these cases as a therapeutic procedure It is difficult to determine how relief is obtained, and it may be largely psychic in character

A peculiar type of obstruction that is occasionally observed is that produced by collapse of the trachea, there seems to be marked softening of the cartilaginous rings The patients frequently have stridor, and periods of marked difficulty in breathing As the instrument enters the trachea, the appearance is similar to that of the esophagus The trachea may resemble the esophagus of a patient who is extremely tense during an esophagoscopic examination In several instances, the symptoms associated with this disturbance have been relieved by bronchoscopic examination

Tumors of the trachea are frequent causes of obstruction, and at this point it is appropriate to emphasize the significance of stridor One is inclined to assume that stridor is produced by some obstruction proximal to the bifurcation of the trachea, and yet this is not always the case Stridor may be present in any type of pulmonary fibrosis, and yet all patients who have stridor should undergo bronchoscopic examination if the larynx is not the source of the difficulty Bronchial obstruction far below the bifurcation of the trachea is sometimes associated

with stridor, and in a case recently observed, stridor was the only physical evidence of the disease in the lung. Roentgenologic examination of the thorax did not reveal evidence of disease. On bronchoscopic study, a carcinoma of the bronchus was found in the depths of the bronchus that runs to the lower lobe of the left lung. Tissue was removed for examination and was found to be that of an adenocarcinoma, grade 1. Stridor has been present in every case of tumor of the trachea that I have observed. In complete stenosis of the bronchus this sign is not elicited. Tumors of the trachea are usually malignant, but in the one case of benign tumor of the trachea in which I have made examination stridor was one of the outstanding signs, and a diagnosis of asthma previously had been made because of this symptom.

External pressure on the trachea may give rise to the same signs and symptoms that are encountered when tumors are intrinsic. This is particularly true of tumors of the thyroid gland, aneurysms of the aorta, and various other types of mediastinal new growth that produce narrowing of the trachea and evidence of obstruction. Granulomatous lesions of the trachea are very rare, and the only one that I have observed was a tuberculoma, which gave rise to marked obstruction. Tumors of all types, in the trachea, manifest themselves by dyspnea and stridor, and examination of the patients otherwise is negative. It is interesting that in these cases of obstruction of the trachea, there is no evidence of emphysema, and one is very prone to overlook the obstruction and to attribute the patient's difficulty to asthma or asthmatic bronchitis.

The most common lesion in the bronchus which produces obstruction is carcinoma, and there are many interesting features in regard to this disease. One is frequently surprised to find extensive clinical evidence of obstruction of the bronchus from carcinoma, and yet, on bronchoscopic examination a lumen of fairly large size is seen penetrating the growth. In the presence of inflammatory lesions or in cases of foreign body, in which the bronchial lumen is much more

completely obstructed, the breath sounds are not likely to be as distant as they are in cases of cancer Emphysema beyond the point of obstruction rarely is present in a case of cancer of the bronchus Atelectasis is frequently seen, and is associated with absence of breath sounds The most significant sign of carcinoma of the bronchus is obstruction of breath sounds If patients give evidence of bronchial obstruction, and cough, pain and dyspnea have been present, even though the bronchoscopic examination may reveal little infiltration in the wall of the bronchus, it is perfectly permissible to remove a specimen of tissue from the bronchial wall In many cases of this type a positive diagnosis can be made by microscopic study of the tissue, although the gross appearance of the lesion would not warrant the diagnosis of carcinoma

In dealing with inflammatory lesions of the lung, especially abscess, obstruction is frequently observed bronchoscopically, and yet there may be no evidence, on general examination, of an obstructive lesion The explanation of the discrepancy in the transmission of sound through the inflammatory and the malignant lesion may lie in the fact that in cases of cancer we are dealing with transmission through a different type of tissue, whereas in cases of abscess there is a more diffuse, infiltrating type of lesion and the sounds are transmitted through the tissue in spite of the bronchial occlusion

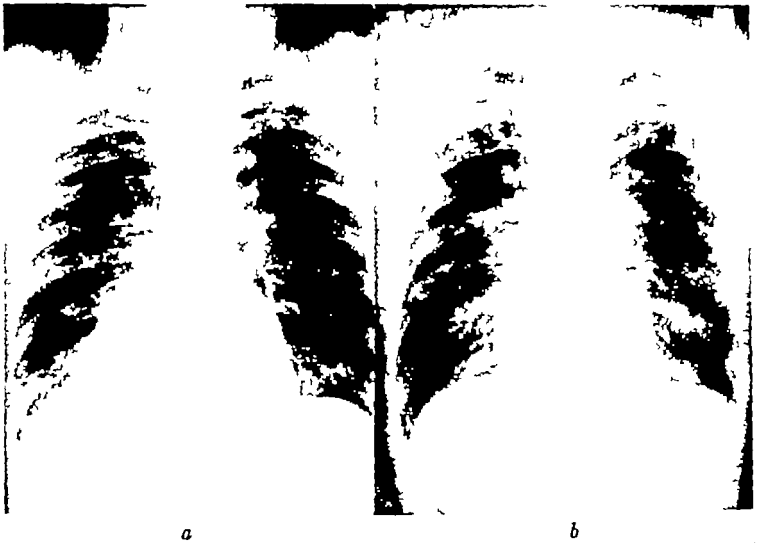
Metastatic carcinomas of the lung rarely involve the lumen of a bronchus and therefore do not give rise to signs or symptoms suggestive of bronchial occlusion In only two instances, at the clinic, have we found metastatic lesions in the bronchial lumen when there was evidence of bronchial occlusion In both of these cases, the original tumor was a hypernephroma In a number of cases, patients have had carcinoma of other organs, but there was little to suggest that the lesion in the lung was metastatic, and we were inclined to regard it as a second primary lesion

Tuberculosis occasionally produces evidence of bronchial occlusion, and we have observed one or two cases of tuberculous ulceration involving the lumen of the bronchus, associated

with pulmonary tuberculosis One of these patients was subjected to bronchoscopy elsewhere, and was thought to have a carcinoma of the bronchus, although the tissue removed for examination was the site of inflammation Tuberculosis of the mediastinal lymph nodes may frequently cause ulceration into the lumen of the bronchus, and although the condition may give rise to definite obstruction that can be recognized bronchoscopically, the findings suggest carcinoma, yet there is lack of evidence of bronchial occlusion on physical examination However, on bronchoscopy, there is very definite infiltration, which may resemble that seen in cases of carcinoma In any case in which there is infiltration at the hilum of the lung on roentgenologic study, and breath sounds are normal, the evidence is that the lesion is inflammatory, probably tuberculous, and not carcinoma In at least 95 to 98 per cent of cases of cancer of the bronchus, evidence of bronchial occlusion is secured on physical examination In cases of bronchiectasis there rarely is any evidence of bronchial obstruction, unless the bronchi are filled with secretion After the pus has been evacuated, breath sounds pass through the bronchi perfectly normally

Foreign bodies frequently produce more or less obstruction of a bronchus, and in almost every case one can detect some difference in breath sounds on the two sides Foreign bodies that are aspirated from the outside, of course, are less difficult to diagnose than those which have their origin within the lung itself In cases in which a calcified hilar lymph node ulcerates through the wall of the bronchus, and produces partial bronchial obstruction and atelectasis the findings are similar to those of cancer and the diagnosis can be made only by bronchoscopic study

Massive atelectasis is attributable to obstruction of a bronchus by tenacious secretion In the early stage of pneumonia one may be dealing with localized atelectasis and in certain cases of pneumonia the early signs are rather bizarre In cases of congenital cystic disease of the lung there may not necessarily be obstruction but physical signs are the same as



a *b*

Fig 50.—*a*, Carcinoma of bronchus, *b*, condition four years after the original treatment by deep roentgen rays

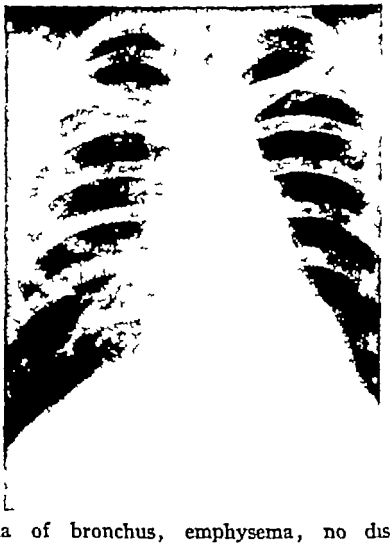


Fig 51.—Carcinoma of bronchus, emphysema, no displacement of the mediastinum

if there were bronchial obstruction Some of our patients were found to have bronchi of fairly normal size, when examined bronchoscopically

The first case by which I wish to illustrate a type of bronchial obstruction, is that of a man who had a carcinoma of the bronchus (Fig 50, *a*) and who was treated by deep roentgen rays Four years after the original treatment, the condition of the lung was improved (Fig 50, *b*)

The second case is that of a man, twenty nine years of age who had a carcinoma of the bronchus associated with emphysema but without displacement of the mediastinum to the unaffected side (Fig 51)

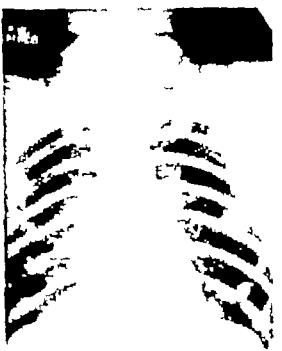


Fig 5 —Tuberculosis of mediastinal lymph nodes ulceration into bronchus terminal tuberculous pericarditis

The third case is that of a patient who was thought to have a carcinoma of the bronchus (Fig 52) and who, on bronchoscopic examination was found to have an ulcerating mass partly occluding the bronchus to the lower lobe of the right lung The tissue removed on several bronchoscopic examinations was reported to have undergone inflammation Death occurred several months later and the patient was found to have tuberculous disease of the mediastinal lymph nodes with ulceration into the bronchus and terminal tuberculous pericarditis

Bilateral bronchial obstruction is sometimes seen in cases

of tuberculous disease in the region of the hilum (Fig 53) The sputum was repeatedly negative for bacilli of tuberculosis,

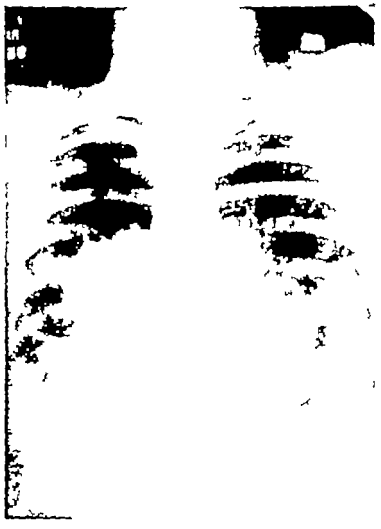


Fig 53 —Bilateral bronchial obstruction in a case of tuberculosis in region of hilum

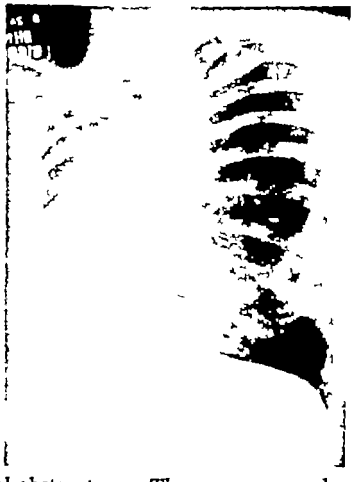


Fig 54 —Bronchial obstruction There were no pulmonary symptoms

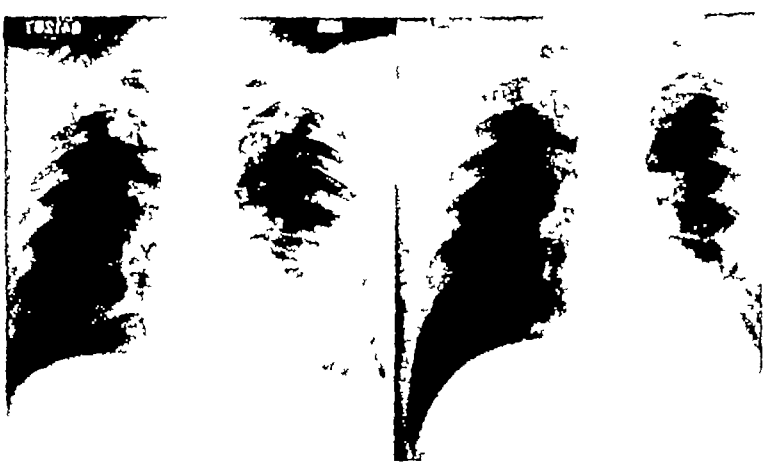
but tissue removed from an ulcerating lesion in the bronchus showed it to be tuberculous in character

a b c

[illegible] deep to exit entire left lun[illegible] b and c beneficial results from bronchoscopic dilatation of stricture

One occasionally may observe bronchial obstruction without pulmonary symptoms (Fig 54) The patient had not had any evidence of pulmonary disease A year after the original examination, she began to have cough and to raise sputum, and on bronchoscopic examination, four years after the original observation, the right bronchus was found to be practically completely obstructed The etiology of the condition was uncertain

In some cases, it is difficult to determine whether the physical signs elicited result from bronchial obstruction or from thickening of the pleura or effusion In Fig 55, *a*, diffuse



a *b*

Fig 56.—*a*, Stricture of bronchus, *b*, result of dilating the stricture

density over the region of the entire left lung is shown Beneficial results were obtained from bronchoscopic dilatation of the stricture (Figs 55, *b* and 55, *c*)

Abscesses in the lung may be insidious in origin, and the history frequently suggests the presence of carcinoma In one case the history suggested the presence of carcinoma, but on physical examination there was no evidence of bronchial obstruction Bronchoscopic study revealed a stricture of a bronchus (Fig 56, *a*) This was dilated and resolution of the lung occurred in six weeks (Fig 56, *b*) Recovery has been complete

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SOME PRACTICAL CONSIDERATIONS OF THE VITAMINS

DWIGHT L. WILBUR

The discovery of the importance of the vitamins in the maintenance of good health has influenced tremendously the practice of medicine. At the present time, although we are in the midst of the development of knowledge in regard to the vitamins, there is obviously much confusion in relation to such considerations as the requirements of man for each vitamin, the relation of the vitamins to resistance against infection, the effect of excessive quantities of vitamins, the part played by the gastro-intestinal tract in conditioning deficiency states, and other significant problems. Unfortunately, much of this confusion will continue and will color medical thought and practice until the chemical identity, requirements, and metabolism of the vitamins are more clearly understood. It seems worth while to point out certain problems which continually confront the physician who is interested in the nutritional status of his patients and to suggest the difficulty of their solution in the light of present knowledge.

The average individual is likely to think of the vitamins as a group of substances perhaps related physiologically if not chemically. However added knowledge continually emphasizes the chemical and physiologic differences of these substances. In two respects all known vitamins are probably similar, and these are that man is dependent on exogenous sources for his supply of vitamin, and that the general physiologic behavior of vitamins is one of catalytic activity.

Our greatest difficulties in understanding vitamin requirements and activity lie in the facts that they are required in

exceedingly small quantities, and until the past year or two we have been unaware of their chemical character In addition, knowledge of the vitamins has in large part been attained as a result of animal experimentation and not through clinical experience

DIFFERENCE BETWEEN VITAMINS AND PROTEINS, FATS AND CARBOHYDRATES

It is important to point out that in many respects the vitamins differ fundamentally from the essential foodstuffs proteins, fats and carbohydrates An enumeration of these differences suggests immediately many of the difficulties which will be encountered in elucidating the exact part the vitamins play in normal and abnormal nutrition

In the first place, man and animals require proteins, fats and carbohydrates in relatively large quantities, at least in appreciable quantities, and these quantitative requirements are fairly well known The requirement for vitamins, on the other hand, is exceedingly small and the actual requirement for each vitamin is unknown, with the possible exception of that for vitamin C Additional confusion is offered because in the absence of clear-cut chemical identification, the vitamin content of food is still classified as excellent, good, or poor, or designated perhaps by a variety of different units (international, mouse, rat, Sherman, and so forth)

In the second place, there exists a variability in supply of the various vitamins, not only because foods differ in their vitamin content from season to season, and from year to year, and because the method of preparation of foods differs, but also there is variability in absorption from and destruction in the gastro-intestinal tract In contrast, the protein, fat and carbohydrate content of foods is relatively uniform and there is also equal uniformity in absorption of these foodstuffs from the gastro-intestinal tract in states of good health In addition, the cooking of food often increases the digestibility, and therefore the assimilation of the so-called essential foodstuffs, although it is likely to impair if not destroy vitamin content

In the third place, proteins, fats, and carbohydrates serve essentially as sources of energy and of material for growth and repair, and as sources of energy present an interchangeability which permits any one of them to serve as the major source of supply. In contrast, vitamins which are essential for growth and other indispensable bodily functions do not serve directly as material for growth or repair, or as sources of energy, and it is of significance to emphasize that there is no evidence of interchangeability of the vitamins, each being required separately from exogenous sources. Again, in a state of good health there is storage of fats and carbohydrates, and there is ample body protein which may serve temporarily as a source of supply, while vitamins, with the exception of vitamin A, are stored in very small quantities only.

Lastly, from the standpoint of studying disease and nutritional states, the physician is at a disadvantage when he looks for evidence of the utilization of the various vitamins by his patient. He may determine rather closely by studies of the basal metabolic rate, the respiratory quotient, and the nitrogenous output in the urine, the various phases of protein, fat and carbohydrate activity, but as yet in the practice of medicine he must estimate the adequacy or inadequacy of the vitamin supply his patient is receiving on the presence of a deficiency disease or by the effect of administration of a specific vitamin.

VITAMIN REQUIREMENT

Clinical experience, widely augmented by and dependent on experimental evidence has clearly established the qualitative requirements of man for vitamins A, B_1, B_2 (G), C and D at some time during the course of his existence. It is possible that other vitamins will be added to this list. While we have a reasonably clear understanding of this qualitative requirement for certain vitamins we have very little evidence of quantitative requirements with the possible exception of vitamins C and D. Experimental evidence suggests beyond question that in addition to a minimal supply there is an optimal level of supply which may be separated from the

minimal level by a fairly wide margin, and also that in the case of certain vitamins (D and perhaps A) there is a level of maximal supply beyond which unfavorable symptoms appear In the words of Sherman, the experimental data indicate that "It seems true of vitamin G as also of vitamins A and C, that the optimal amount is much higher than the minimal ('actual') requirement, that is, that the body is able to make good use of a much more liberal intake than can be proved absolutely necessary" This suggests that the difference may be experienced as a state of "passable" in contrast to "buoyant" health While this sounds reasonable when applied to man it remains as yet unproved in clinical medicine

Our failure to know the quantitative requirements of our patients for vitamins, as well as the quantity of the vitamins in different foods, is still the barrier which separates fact from opinion in regard to the frequency and nature of vitamin deficiency states, with the exception of rickets, in the American people We are still largely dependent on the occurrence of a deficiency disease to recognize that a patient has received an inadequate supply of vitamins While vitamin deficiency diseases with the exception of rickets, apparently are rare in this country, vitamin deficiency states or partial deficiency states may exist, since it is readily conceivable that while many persons are ingesting enough (minimal requirement) of the vitamins to keep them from getting deficiency disease they may not be getting enough (optimal requirement) to keep them in a state of "buoyant" health It is in the group between these two levels that we must expect to find the majority of persons in this country who have inadequate intake of vitamins

OCCURRENCE OF VITAMIN DEFICIENCY

Every wise clinician is continually on the lookout for vitamin deficiency states among the patients he sees, and not infrequently he may become conscience stricken for fear that he is not recognizing deficiency states The public, on the other hand, is constantly reminded by advertising specialists that failure to eat daily, in abundant quantities, this and that

vitamin-containing food, will lead to a variety of diseases, while those who partake of the food are promised a Utopia of health Obviously the public and even the physicians become confused eventually, particularly because of the lack of evidence of clear-cut symptoms and signs and of experience to prove or disprove the assertions that are made

Experience indicates that with few exceptions most deficiency diseases observed in hospital wards and private practice are not clear cut We are likely to think of xerophthalmia, beri beri, pellagra, and scurvy as clear-cut entities largely because they can be produced in the experimental animal with some degree of constancy However as McCollum has pointed out, it is questionable if a pure vitamin deficiency state, with the possible exception of scurvy, ever has been produced in the experimental animal Consequently, it can be anticipated that few deficiency diseases of man will be clear cut, and this is actually the case

As previously mentioned with the exception of rickets, recognizable deficiency diseases are uncommon in the United States There is a suggestion that states of vitamin A and C deficiency may be much more widespread than is indicated by the incidence of scurvy and xerophthalmia Jeans and Zentmire, in studying the sensitivity to light following partial adaptation to dark of a group of children found 20 per cent of the group with subnormal adaptation one half were relieved promptly by the administration of cod liver oil The authors interpreted this as evidence of an abnormality attributable to deficiency of vitamin A, previously unknown and unrecognized by the patients Further proof must be forthcoming before this important suggestion can be established as a fact Dalldorf, who is one of those who believes the capillary resistance test may be used as an index of subclinical scurvy, has reported that children from poor homes in New York State show an incidence of 55 to 60 per cent of positive tests Schultzer has reported that of the hospital patients in Denmark whom he studied 20 per cent gave positive tests suggesting C vitamino sis However the capillary resistance test is

not uniformly accepted as being of value in determining latent or subclinical scurvy, and consequently results such as these will require further confirmation

Until more facts are available, it seems reasonable to assert that the present evidence indicates that states of latent or subclinical vitamin deficiency are not widespread in this country, but that as yet assertions in this regard are matters of opinion and not of fact

METHODS BY WHICH VITAMIN DEFICIENCY DISEASES ARE PRODUCED

In the past, probably too much emphasis has been placed on the conception that dietary deficiency diseases arise solely from lack of sufficient quantity of certain essential food factors in the diet While undoubtedly this is the common cause of such clinical and experimental deficiencies, it must be emphasized that deficiencies may also result from failure of adequate absorption or utilization of vitamins or foodstuffs On the other hand, there may be an increased demand for and consumption of vitamins, for example during periods of growth, pregnancy, or disease, especially severe infections, and when the basal metabolic function is enhanced All of these factors may explain a deficiency state in the presence of an apparently adequate supply of vitamins

The importance of the gastro-intestinal tract in relation to the development and occurrence of deficiency diseases is being continually emphasized In recent years, studies have led to the inclusion of pernicious anemia, polyneuritis accompanying pregnancy and alcoholism, and the toxemia occurring in pernicious vomiting of pregnancy and in intestinal obstruction as deficiency states conditioned or significantly accompanied by gastro-intestinal disease Night blindness, beri-beri, pellagra and tritional edema also have been observed to affect patients who partook of an apparently adequate diet but who were unable to assimilate a sufficient amount of foodstuffs because of organic gastro-intestinal disease It seems reasonable to think that in this country a large proportion of deficiency

states must arise from this cause since in general the diet of the average American is probably adequate in its qualitative and quantitative aspects It is possible that if widespread economic distress continues, malnutrition will become much more common in the United States than it is at present

Attention should be called to our lamentable lack of information in regard to alimentation There is need of additional facts secured through new methods of attack, on the problem of alimentation and absorption before we shall have a complete understanding of the mechanism of production of deficiency diseases At present it is recognized that the changes in the gastro-intestinal tract which may lead to the development of such conditions include atrophy of the mucous membrane, changes in secretion of normal digestive juices or other substances, absence of bile salts, loss of normal gastro-intestinal secretions, as in diarrhea and vomiting, and, lastly, mechanical factors which obstruct or prevent contact of foods with a sufficient area of intestinal mucosa to permit adequate absorption

The studies of Castle Townsend and Heath indicate that pernicious anemia is a previously undescribed deficiency disease in which the deficiency is the result not of a deficient diet, but usually of the absence from the gastric juice of a specific factor which is not hydrochloric acid, pepsin, rennin or lipase There also have been described a number of conditions identical with pernicious anemia affecting individuals with various organic abnormalities of the digestive tract Examination of the gastric juice of some of these individuals has revealed the presence of the so-called intrinsic factor of Castle and his associate

Night blindness attributable to deficiency of vitamin A apparently the result of inadequate absorption of the vitamin in the presence of a gastrocolic fistula which subtracted the small intestine has been reported by Futterman and me An instance of beriberi following entero-enterostomy in which all but 24 inches of the small bowel was subtracted has been recorded by Lynch and his associates Of interest in this case

is the fact that when yeast was administered considerable relief was obtained, but complete relief did not occur until the long loop of small bowel had been restored to normal sequence There are in the literature numerous reports, such as that of Eusterman and O'Leary, of pellagra occurring in gastro-intestinal disease, particularly in cases of carcinoma of the stomach with obstruction

Although factors of intestinal absorption undoubtedly are exceedingly important, as has been stressed, attention should also be called to the fact that deficiency states may develop in patients with gastro-intestinal disease, who as a result of symptoms or poor advice partake of an inadequate diet The occasional development of scurvy by patients under treatment for peptic ulcer is a good demonstration of this fact

EFFECT OF CONSUMPTION OF EXCESSIVE QUANTITIES OF THE VITAMINS

The preparation for oral and parenteral administration of concentrated and crystalline forms of the various vitamins has raised the problem of the possibility of toxic effects from excessive dosage The evidence presented to date suggests that toxic effects occur in man after the administration of excessive quantities of vitamin D only While Davis and Moore have reported that massive doses of vitamin A given to young rats resulted in emaciation, hemorrhagic retinitis, and loss of hair about the mouth, adverse effects on man have not been reported, and the work of the authors suggests that the margin of safety is very wide Excessive doses of vitamin B, C and G have not been reported to produce unfavorable symptoms in man or animals Much has been written in regard to the toxic effects of irradiated ergosterol These effects result from improperly irradiated ergosterol or from excessive quantities of the vitamin itself In discussing the symptoms produced in man as a result of over-dosage of viosterol, Reed pointed out that in his studies of 300 subjects, toxicity in man may be recognized very early by the subjects themselves and before any serious damage has resulted The initial symptom is most

commonly increased frequency of urination Anorexia and nausea also occur, and thereafter acute gastro-intestinal symptoms without fever Muscular weakness, lassitude, dull aching in muscles, dizziness disturbed muscular coördination and faulty equilibrium may develop The minimal toxic dose is stated to be 150,000 international units daily (Reed) and 10,000 such units daily (Harris) Since the optimal therapeutic dose in the treatment of rickets is 3,000 to 5,000 units daily, there is a margin of safety which may easily be maintained, and yet, through carelessness, may be exceeded

In summarizing the evidence it seems fair to state that with the possible exception of vitamin D there need be little concern at present over the toxic effects of administration of excessive amounts of the vitamins

VITAMINS AND RESISTANCE TO INFECTION

The relation of resistance against infection to an adequate supply of vitamins is a problem of great practical significance Members of the public at large as well as physicians, are being continually bombarded with advertising of the "anti infective" power of foods or drugs containing this or that vitamin It seems that the important practical problem is not so much whether an individual on an inadequate diet is less capable of resisting infection than is a normal individual but whether amounts of vitamin in excess of those normally obtained by well nourished persons will further increase resistance to infections While there are some studies which tend to suggest that added amounts of vitamin do increase resistance to infection, the whole evidence on this problem is of such conflicting character that much more information is needed before the question at issue can be answered The evidence has been well summarized in an editorial in the *Journal of the American Medical Association* Despite the many demonstrated correlations between lack of an essential dietary factor and functional and structural change in the organism there is surprisingly little cogent evidence of a specific relation between these factors and infection

In states of deficiency Clausen reported the evidence to show that "a deficiency of vitamins A and C appears quite definitely to lower resistance to infection In certain cases a lack of the vitamin B complex may do the same thing A lack of vitamin D cannot be said to have a proven effect in lowering resistance It seems probable that the existence of a partial deficiency of vitamins may result in loss of resistance to in fection, though this cannot be said from the present evidence, to have been clearly established"

It is very questionable, therefore, at the present time, whether the administration of vitamin preparations to the average well-nourished individual is of any value in increasing his resistance or in decreasing his susceptibility to infection

ADVISABILITY OF INCREASING THE VITAMIN CONTENT OF FOODS

Widespread attempts to increase the vitamin content of foods have been limited largely to increases in vitamin D con tent of infant foods and milk There is much discussion of the advisability of supplementing or increasing the vitamin D content of milk because of the frequency of rickets One difficulty which has arisen in experimental work on vitamin D is that animals do not utilize different antirachitic materials in the same proportions This variability, which is still an unex-plained phenomenon, may possibly be attributable to chemical differences in antirachitic agents Friedman's studies indicate that far fewer units of vitamin D in the form of vitamin D milk are required to protect against or to heal rickets than are required of other antirachitic agents Of the various methods of augmenting the vitamin D content of milk, the most satis-factory are direct irradiation of the milk and direct addition of vitamin D concentrate to milk The practicability of supple-menting milk with vitamin D has been demonstrated, and its advisability reasonably well established in the demonstration that most cases of rickets could be cured by substituting such milk for other milk in the diets of children

USE OF DIETS HIGH IN VITAMIN CONTENT AND VITAMIN CONCENTRATE

Foods high in vitamin content are obviously very useful in the treatment of deficiency diseases. Whether they are of value to individuals who are 'below par' chronically fatigued, and in poor health, or who are the victims of many chronic diseases not involving the gastro-intestinal tract, and yet who are without definite evidence of a deficiency state is questionable. So many factors enter into the practice of medicine that it is difficult under the circumstances mentioned to conclude that improvement experienced by such patients on a diet high in vitamin content is the result of this diet alone. There is, on the other hand, no real objection to the use of this type of diet for patients of the type mentioned, so long as a conservative attitude is taken in regard to the benefits to be derived from the high content of vitamins. The most practical value for a diet high in vitamin content lies in the treatment not only of patients with deficiency states but also of those who for a considerable period of time have subsisted on a diet qualitatively limited in its vitamin content.

The preparation of crystalline products and concentrates of some of the vitamins as well as the synthesis of others, has made available a method of administration of vitamins other than through the consumption of food. We are not in a position, as yet, to evaluate the use of these substances clinically. Danger of administration of excessive quantities, particularly of vitamin D, must be considered. It seems reasonable at the present time to reserve their use for patients with deficiency states in treatment and prevention of rickets, in certain instances in pregnancy and dental caries, and for purely experimental purposes. The preparation of products which may be used parenterally will be of distinct aid in the treatment of deficiency states of patients with gastro-intestinal disease.

MISCELLANEOUS OBSERVATIONS

Another point of practical value is frequently to recall to mind the situations under which one is most likely to observe

the development or occurrence of deficiency states One should be on the lookout for them among patients who have chronic obstructing and diffuse ulcerating lesions of the gastro-intestinal tract or other conditions which interfere with normal gastro-intestinal activity, among those who are in a state of malnutrition, among those who are mentally deficient and, lastly, among those who have not been able to get fresh foods for a long time

The influence on absorption of hydrocarbons, such as those in liquid petrolatum, has been carefully studied because of the suggestion that liquid petrolatum may seriously interfere with absorption of vitamins While Dutcher and his collaborators have found some experimental evidence to indicate that absorption of carotene may be interfered with to a slight extent, this does not hold true in the case of vitamin A, because this vitamin has greater solubility in the liquids of the intestinal juice than it has in the hydrocarbons of liquid petrolatum

SUMMARY

In considering nutritional problems which involve the vitamins, it is important to remember that the vitamins differ fundamentally in many respects from proteins, fats and carbohydrates

Although we have a fairly clear conception of the qualitative requirements of the vitamins, our knowledge of the quantitative requirement of man for them is exceedingly meager, and this influences greatly our ability to solve many of the nutritional problems with which we are frequently confronted If we accept the experimental evidence that there exists an optimal as well as a minimal or actual requirement of one or all of the vitamins, then our problems are still further enlarged and confused

With the exception of rickets and pellagra, especially in areas where the latter is endemic, recognizable deficiency diseases are probably uncommon in the United States Until more facts are available it seems reasonable to assert that the present evidence indicates that states of latent or subclinical

vitamin deficiency are not widespread in the country but that as yet assertions in this regard are still matters of opinion and not of fact.

It seems reasonable that in this country a large proportion of deficiency states which develop will be the result of mechanical or chemical alterations in the gastro-intestinal tract which interfere with adequate alimentation although the diet is adequate in nutritional requirements

At present the evidence indicates that with the possible exception of vitamin D there need be little concern over the toxic effect of administration of excessive amounts of the vitamins

It is questionable if administration of amounts of vitamin in excess of those normally obtained by well nourished persons is of any value in further increasing resistance or diminishing susceptibility to infections Although there is no apparent objection to the widespread use of diets high in vitamin content, a conservative viewpoint should be adopted in regard to their value in the treatment of a variety of conditions not clearly the result of a deficient intake of vitamins

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VITAMINS FROM A CHEMICAL VIEWPOINT

EDWARD C KENDALL

During the past fifty or sixty years chemists have developed the field of organic chemistry A vast number of new substances have been synthesized some of them had been found in nature but most of them were new For example, compounds which contain two benzene rings combined with an oxygen bridge had been known for many years In 1926 Harrington showed that this structure occurs in thyroxin although up to this time this grouping had never been known to occur in nature. As the more complicated biologically active compounds have been isolated we find that they are related to compounds already made by organic chemists During the past few years, as more and more complicated compounds have been isolated, it is very interesting to note that some substance closely related is already well known It is only during the past few years that the chemist has been able to reach out and make a bridge between the vitamins and this mass of organic substances that have been prepared synthetically

The study of the vitamins has passed through the three stages of investigation which must be followed for all physiologically active compounds It first was shown that vitamins existed this was followed by their isolation in pure form finally by their identification and, in one case, by synthesis

Data which proved the existence of essential constituents which occur in foodstuffs were first contributed by those interested in problems of nutrition and clinical medicine One of the most outstanding contributions was made by Captain Cook who prevented scurvy on shipboard by the use of a proper diet More recently the nutritional studies of Hopkins

and the clinical investigation of Eijkman in the determination of the etiology of beri-beri indicated the strong probability that in foodstuffs certain substances are present which are essential for normal well-being Finally this group of compounds was given the name vitamins by Casimir Funk in 1911 The next few succeeding years witnessed the rapid separation of unknown products in foods which were added to the list of vitamins in alphabetical order

McCollum and Simmonds showed that the absence of a constituent of certain fats prevented the growth of the animal and produced the condition of dryness and soreness of the eyes known as xerophthalmia Since 1916 this food accessory has been designated fat-soluble vitamin A At the same time, McCollum also showed that there was present in food a water soluble compound which was essential for growth This was called water-soluble B Further investigations revealed the fact that absence of water-soluble B not only retarded growth but produced a condition of weakness of muscles and a peculiar tetany and spasm, polyneuritis

That scurvy was attributable to the deficiency of a product occurring in food was shown by the production of the disease in guinea pigs when kept on a diet of dried milk and oats Symptoms of rickets were produced in rats and other experimental animals with diets which did not contain a proper ratio of calcium and phosphorus and which also were lacking in the food accessory, vitamin D, which was found in cod liver oil and other fatty foodstuffs

Evans and his coworkers added another vitamin essential for reproduction which was shown to be present in lettuce and in wheat germ oil This was designated vitamin E Finally the disease long known as pellagra was identified as a food deficiency disease which could be cured by administration of a substance present in yeast This compound is soluble in water, and therefore occurs as a constituent in the so-called water-soluble vitamin B It therefore became necessary to redesignate the water-soluble products other than the substance the lack of which produces polyneuritis, either as B_1,

B_2, B_3, B_4, or else to give them other letters In England the use of the subnumerals of B was adopted and the factor which cures pellagra was called B- In the United States it was decided to designate this vitamin by the letter G

At the present time it seems highly probable that there are present in the water soluble fraction of yeast other substances which are essential and which should be designated either as B_3, B_4, and so forth, or which should be given letters H, I, J Up to the present, however, these substances have not been isolated in pure form.

VITAMIN A

The first evidence which indicated the nature of vitamin A was contributed by Steenbock and coworkers They showed that a correlation existed between the vitamin A content of foodstuffs and the presence of yellow pigments, yellow corn meal contained more vitamin A than did white cornmeal This work could not be confirmed by Drummond and MacWalter because of variations in other vitamins but it later was confirmed through the investigation of Moore The association of vitamin A activity with colored pigments was then actively investigated with the result that carotene was shown to be the precursor of vitamin A

Carotene is a compound found widely distributed in nature, possibly most easily recognized in carrots, the yellow color of which is attributable to its presence Carotene was known to contain only carbon and hydrogen and it has been shown to break up rather easily on oxidation When carotene was fed to an animal that had been maintained on a diet deficient in vitamin A it was shown that the adsorption spectrum of carotene in the liver disappeared and the presence of vitamin A could be shown The animal was relieved of vitamin A deficiency Drummond then showed that vitamin A could be distilled and that the distillate contained an alcohol of high molecular weight

The evidence which related vitamin A to carotene indicated the necessity of a careful chemical investigation of the nature of the compound The chemical nature of both carotene

and vitamin A has been established by the work of Karrer and coworkers They have shown that carotene contains a long chain of eighteen carbon atoms Between each two carbon atoms is a double bond and four methyl groups are placed symmetrically on the long chain At each end of the chain there is a partially reduced, six-membered ring, which also bears three methyl groups Cleavage of this structure between the ninth and tenth carbon atoms of the long chain, with an alcohol group attached to each portion, gives two molecules of vitamin A The molecule of vitamin A, therefore, contains a six-membered ring to which is attached a side chain of nine carbon atoms which contains four double bonds and which is terminated with a primary alcohol group Carotene is easily acted on by oxidizing agents, it is sensitive to molecular oxygen and air It is therefore not surprising that vitamin A is also easily oxidized and can be destroyed with mild oxidation The presence of the many double bonds renders chemical investigation, and in particular the synthetic production of vitamin A, an exceedingly difficult matter Certain derivatives have been prepared, however, by Karrer which contain the essential ring structure and with the double bonds in the side chain removed by reduction with hydrogen Such a compound has been prepared synthetically and has been shown to be identical with the substance obtained by reduction of vitamin A

The identification of the structure of vitamin A affords all the necessary information to permit a pharmacologic investigation of this important vitamin and closely related compounds The quantitative assay of foodstuffs and biologic products which are a source of vitamin A is now placed on a firm basis Vitamin A is widely distributed in nature particularly in certain fish oils and it appears probable that the amount is adequate for medicinal needs It will, however, be a matter of great satisfaction to prepare vitamin A synthetically This step, although it will probably be attended by great difficulties, is essential in order to prove conclusively that the structural formula assigned is correct It is also possible that a synthesis

will be devised which will afford an inexhaustible supply of vitamin A and make it available at a greatly reduced price

VITAMIN B

One of the most distressing diseases in certain parts of the Orient is beri beri and one of the most significant contributions which biochemical investigation has given to medicine consists in the proof that beri beri is caused by a deficiency of a food accessory, vitamin B The history of the investigation of beri beri is a most interesting romance but the history of the isolation of the vitamin which cures the disease is equally fascinating After treatment of enormous amounts of rice hulls, Jansen and Donath succeeded in isolating the vitamin in crystalline form and through the use of a bird native to Java they proved that polyneuritis could be cured by the administration of the crystalline vitamin Seidell also carried out a large amount of work starting with yeast

Williams and coworkers[7,8] have maintained a persistent attack on the problem for many years and recently their method of isolation of the crystalline vitamin has yielded sufficient material for its identification It has been shown to consist of a single molecule $C_{12}H_{18}ON_4S$, which may be quantitatively split with sodium bisulphite into two crystalline substances, one with acidic and one with basic properties These two substances are $C_6H_8N_2SO$ and C_6H_9ONS As this article is written the final investigation concerning the structure of these two crystalline compounds is being conducted and there is no doubt that within the very near future the exact structure of vitamin B will be established It is probable that the compound may be synthesized, although it will be a difficult task The wide distribution of vitamin B affords a ready supply and synthesis is not necessary in order to provide an available source of the vitamin

VITAMIN C

The identification of vitamin C was due to the efforts of Albert Szent Gyorgyi For many years he carried out an in

vestigation in the field of biologic oxidation and reduction He finally showed that there was present, widely distributed in fruits and plants, a substance which he described as a reducing factor It possessed the ability to reduce silver nitrate in a neutral solution He then isolated a compound from the suprarenal glands and showed that it was identical to the reducing factor present in plants Analysis of the crystalline compound showed that it was related to the sugars, although it possesses acidic properties It was provisionally named "hexuronic acid" and was regarded as probably related to glucuronic acid although it possessed physiologic properties not found in any of the sugar acids Finally, 1932, Svirbely and Szent-Gyorgyi[6] showed that hexuronic acid was in fact vitamin C

For many years, C C King had investigated the chemical properties of vitamin C In 1931 and in the early part of 1932 he finally succeeded in crystallizing vitamin C and then showed that the crystals of vitamin C were identical with Szent-Gyorgyi's hexuronic acid The two separate investigations, one working for the identification of a definite crystalline substance and the other using concentrations of vitamin C in animal experimentation, finally culminated in the evidence that crystalline vitamin C and crystalline hexuronic acid were one and the same thing and established the identity of vitamin C beyond controversy All investigators in the field have accepted the evidence as proof that vitamin C is hexuronic acid

As soon as it was shown that hexuronic acid cured scurvy, Szent-Gyorgyi named the compound ascorbic acid For this same substance the Council on Pharmacy and Chemistry of the American Medical Association has recently seen fit to coin still another name, Ce-Vitamic Acid Beside these names there are several proprietary names which describe the compound as it is prepared by various pharmaceutic manufacturing houses

Chemically, vitamin C consists of a straight chain of carbon atoms similar to the chain of carbon atoms found in glucose

At one end of the chain there is a carboxyl group which forms a lactone with a hydroxyl group on the third carbon from the carboxyl This lactone is quite stable and is not responsible for the acidic properties of the compound The acidic properties are due to two hydroxyl groups which occur on the two carbons adjacent to the carboxyl because of a double bond which lies between the alpha and beta carbons On the fifth and sixth carbons are two hydroxyl groups which readily form a derivative with acetone It was through the preparation of the acetone derivative that Svirbely and Szent Györgyi and Vargha were able to separate ascorbic acid in pure form and prove that the physiologic activity was due to the six-carbon compound and not to any other adsorbed substance

Vitamin C possesses striking properties in relation to oxidation and reduction and its function in the body is undoubtedly related to its effect on the processes of oxidation Starting with glucose, ascorbic acid has been prepared synthetically It has also been produced by Haworth and coworkers through the addition of a sixth carbon to the five-carbon sugar, xylose There are two optically active forms, dextro and levo The material occurring in the levo form is the natural product The dextro form is not active in the treatment of scurvy The preparation of pure ascorbic acid is important in medicine because it permits the intravenous injection of known amounts of material into patients and infants who are deficient in this substance The chief source of the material today is a pepper grown in Hungary but it seems highly probable that synthetic methods will be devised for the commercial preparation of this interesting compound

VITAMIN D

One of the diseases which can be traced back to the earliest historical times is rickets Although the disease has been controlled for many years through the administration of cod liver oil it was a matter of great importance to isolate and prove the nature of the active constituent in cod liver oil responsible for the physiologic activity After it had been shown that the

active material was not affected by formation of the soap from the fats in cod liver oil, its separation in highly concentrated form was made possible The final proof of the structure of vitamin D, however, was not furnished by isolation of the vitamin in pure crystalline form, it was rather through a fortuitous association of irradiation and the cure of rickets Steenbock and coworkers, and Hess, showed that irradiation of certain foodstuffs resulted in the production of physiologic activity similar to that of cod liver oil This was soon extended to the observation that the precursor of the active compound which was affected by irradiation was a sterol Windaus then supplied the essential contribution that the specific member of this large family of compounds was ergosterol, which when irradiated gives the maximum vitamin D activity The treatment of rickets and the identification of the essential vitamin, therefore, is reduced to the problem of determining the influence of ultraviolet light on certain sterols and in particular on ergosterol

The sterols form a large family of substances all of which contain three six-membered rings and one five-membered ring Attached to the five-membered ring is a side chain of about nine atoms of carbon Members of the sterol family differ from one another in the number and position of double bonds and in the groups attached to the four-ring system Although there is good evidence that the effect of ultraviolet light on ergosterol is due to the change in position of two of its three double bonds, there are still some problems in regard to the details of its structure which will require further work The number of possible compounds containing such a large number of carbon atoms, and the fact that such a large number of sterol isomers is possible, make investigation in this field very difficult and time-consuming The importance of the problem, however, is immediately apparent and the recent work on the male and female sex hormones, on the active agent of corpus luteum, and on the active principle in digitalis, all go to show that this group of compounds is utilized by the animal organism in a wide variety of ways A chemical investigation of

this large family of compounds furnishes a challenge to the chemist, which has been accepted and which will yield results of greatest importance

VITAMIN E

Little is known of the exact chemical nature of vitamin E except that it is a fat-soluble substance and may be another member of the sterol family

VITAMIN G OR B_2

The solubility of vitamin G or B_2 necessitates its removal from the large group of substances soluble in water, which are present in yeast Because of the close similarity in the solubility of vitamin G and the flavins, the two products are found closely associated in extracts from yeast milk, or liver The results of certain investigations indicated that vitamin G probably was identical with lacto-flavin A very recent paper by Ehrhjem and Koehn indicates that this apparent identity is only a coincidence and that lacto-flavin can be quantitatively separated from vitamin G The same group of investigators has carried out the investigation to an advanced stage and chemical identification of vitamin G appears to be close at hand

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CLINICAL AND ROENTGENOLOGIC COMMENTS ON CALCAREOUS AORTIC STENOSIS

FREDRICK A WILLIUS AND JOHN D CAMP

Until the last few years recognition of calcareous aortic stenosis was practically limited to postmortem examination During the last four or five years the condition has been identified from time to time during the life of the patient, and more recently, its recognition has been practically a routine procedure It has thus been demonstrated that a lesion, which formerly was thought to be of rare occurrence, is not uncommon, and careful clinical and roentgenographic study has evolved a series of facts that permits its recognition without difficulty During the last few months, twelve cases of calcareous aortic stenosis have been recognized Three additional cases, which were observed several months earlier, are included in this report The diagnosis in all cases was verified by special roentgenologic study, and in four other cases, the roentgenologist demonstrated calcareous aortic valves, during routine fluoroscopy for other conditions

Mönckeberg, in 1904 described the pathologic lesion and in 1929 Margolis Zielles en and Barnes reported their results of a study of forty-one cases that came to necropsy In 1931, Christian, in a splendid article clearly postulated pertinent facts regarding the clinical recognition of calcareous aortic stenosis and made the following prediction "From observing the calcareous deposits in these heart valves it is evident that roentgenography with proper technic should often demonstrate the calcification in the living patient"

The purpose of this report is to summarize the diagnostic criteria and to emphasize the importance of roentgenoscopy

in the verification and recognition of this lesion In the fifteen cases which comprise this report, Dr Camp was able to demonstrate the calcareous changes in the aortic valves by roentgenologic methods Thus far, his record is perfect

The clinical syndrome of calcareous aortic stenosis is so definite that its clinical recognition should without doubt be a

TABLE 1

SEX INCIDENCE

Author	Males.		Females	
	Number	Per cent	Number	Per cent
Cabot	25	89	3	11
Margolis and others	34	83	7	17
Christian	15	71	6	29
Willius and Camp	13	87	2	13
Total	87	83	18	17

TABLE 2

AGE INCIDENCE

Author	Age periods years			
	20 to 29	30 to 39	40 to 49	50 or over
Cabot		5	7	16
Margolis and others	1	2	3	35
Christian	1	4	3	13
Willius and Camp	1	1	1	12
Total number	3	12	14	76
Total per cent	2 9	11 4	13 3	72 4

routine procedure The features of this syndrome are as follows (1) It occurs predominantly among men who are beyond the fiftieth year of life (72 per cent of reported cases) The sex and age incidence are shown in Tables 1 and 2 (2) The lesion in very slowly progressive, and results in cardiac

failure relatively late in its course Death usually occurs with the syndrome of congestive heart failure, although death occasionally occurs very suddenly (3) A loud, rough, systolic murmur is heard over the aortic area, at times, it is audible over the entire cardiac area (4) A systolic thrill is palpable over the aortic area at times, it is palpable only when the patient bends forward It may be absent temporarily during the stage of cardiac failure and reappear when cardiac function improves (5) A soft, blowing diastolic murmur, the murmur of aortic insufficiency at times occurs (27 per cent of present series) (6) The absence or diminution of the aortic second sound is a very important diagnostic sign (7) Considerable cardiac hypertrophy occurs, the degree of course varying in different cases (8) In the cases that are unassociated with aortic insufficiency and hypertension, the pulse is small and the pulse pressure is normal *or diminished* (9) There is an absence of consistent data which might indicate the etiology of the lesion (10) At necropsy, the heart is found to be increased greatly in weight, and the aortic valves are narrowed greatly by cohesion of the leaflets and by deposition of calcium The other valves invariably are normal

The etiology of calcareous aortic stenosis is still obscure The hypotheses that have been advanced include (1) that it is the result of rheumatic fever,[1 2 3] (2) that it is part of a degenerative process, with the secondary deposit of calcium, (3) that it is a healed lesion of subacute bacterial endocarditis, (4) that it is the result of a general toxic or remote infectious process (5) that it is the result of an inflammatory lesion of the vessels of the aortic valve ring and leaflets, and (6) that it is of unknown etiology As the various hypotheses are analyzed with the composite data of the reported cases in mind, one is forced to the conclusion that the etiology of this peculiar lesion is still very uncertain In seventy seven cases that have been reported a history of rheumatic fever was elicited in only sixteen cases (21 per cent) This represents a very small incidence when compared to the incidence of a positive history in acknowledged cases of rheumatic valvular

defects The character of the lesion, and its massive deposit of calcium are vastly different from rheumatic lesions of other valves, and of the aortic valve The strikingly solitary occurrence of the lesion militates against a rheumatic etiology, as the clear-cut rheumatic aortic lesion frequently occurs in conjunction with a defect of the mitral valve Likewise, the rare occurrence of pericarditis tends to argue against the rheumatic etiology Further contradictory evidence is presented in the predominant occurrence among males and in its only casual appearance among young individuals

Fig 57 —Specimen obtained at necropsy, showing changes associated with calcareous chronic aortic stenosis

In considering the lesion as degenerative or arteriosclerotic, numerous objections can be submitted The lesion occurs without marked arteriosclerotic changes elsewhere, and frequently, the aorta itself is entirely uninvolved The incidence of coronary sclerosis does not differ from that among other patients who are the same age The occasional occurrence of the lesion among young individuals, especially in the third decade of life, strongly argues against a purely degenerative process (Fig 57)

That calcareous aortic stenosis represents the healed stage

of subacute bacterial endocarditis fails to find confirmation in the absence of a history of prolonged febrile illness and in the absence of healed embolic visceral lesions at necropsy

That the lesion represents the healed stage of an inflammation is probable, but its exact etiology still remains problematic It may be the direct result of bacterial invasion or it may be the result of toxins, in cases in which the initial insult to the valve is slight and does not produce distinctive clinical manifestations In these cases the signs and symptoms of heart failure occur late, and are consequent to the developing stenosis Little or no knowledge of the early lesion or its genesis is available and the reason for this probably lies in the fact that death rarely occurs at this period

The electrocardiogram usually exhibits abnormalities, which are not necessarily characteristic In this series, changes occurred in thirteen cases (87 per cent) Changes in the T wave occurred in thirteen cases as follows T wave negativity in lead I, six cases, T wave negativity in leads I and II, four cases, T wave negativity in all leads, one case, diphasic T waves in leads I and II, one case and diphasic T waves in lead II and negative T waves in lead III, one case Bundle branch block occurred in three cases and complete heart block in two cases

During routine fluoroscopy, Dr Camp found calcification of the aortic valves in four cases In three of these cases, the patients were men, and in the other case the patient was a woman These patients were fifty nine sixty three, sixty five, and seventy two years of age respectively One patient had a systolic aortic murmur but none presented evidence of aortic stenosis or cardiac failure We feel certain that these cases represent calcification of the aortic valve leaflets a different entity than those cases which form the basis of this study

The first and fundamental work concerning the roentgenologic recognition of calcification of the heart was reported in 1905 by Symmonds who studied roentgenographically at necropsy the hearts of five patients He classified the location of cardiac calcification as follows (1) pericardial, (2) endo-

cardial, (3) myocardial, and (4) arterial (coronary) It was not until 1922 that Klason reported the first case of cardiac calcification that was recognized roentgenologically in vivo, although at necropsy the calcification was found to be in the mitral valve instead of in the pericardium, as had been supposed

In 1924, Cutler and Sosman reported four cases of cardiac calcification, which were observed at necropsy In three of these cases, the pericardium was involved, and in the other case, the aortic, mitral and tricuspid valves were involved In none of these cases was the condition recognized roentgenologically, before death In a fifth case, which was reported in this series, calcification of the mitral valve was observed fluoroscopically in vivo but the patient could not be traced and final proof was lacking In 1925, Fleischner reported a case of calcification of the annulus fibrosus, which was confirmed by necropsy In 1931, Christian called attention to the clinical syndrome of calcareous aortic stenosis and reported the first case in which the calcified valves were recognized antemortem, by the roentgenologist (Sosman) In 1913, Parade and Kuhlmann recorded one case of calcification of the aortic valve and four cases of calcification of the mitral valve, all of which were recognized roentgenologically before death Later, in the same year, Sosman, whose interest in the subject had been aroused by his earlier observations and by Christian's cooperation, reported, with Wosika, twenty cases of calcareous aortic stenosis and nineteen cases of calcification of the mitral valve, in all of which the calcification was observed roentgenologically before death The large number of patients which were seen by these authors in such a comparatively short time may be explained by the early recognition, by these investigators, of the importance of roentgenoscopy in examination of these patients

We know that the cardiac area in these cases must be scrutinized carefully under the roentgenoscope, by using a small aperture in order to detect accurately the presence of calcium The dancing nature of the calcified valve shadows,

as they move in the blood stream, is characteristic and their situation should readily determine whether they are associated with the aortic or mitral orifices The aortic shadows are best seen with the patient in the right anterior oblique position since in the anteroposterior view they are frequently obscured by the spinal column Because of their rapid motion, these shadows cannot be clearly recorded in roentgenograms unless

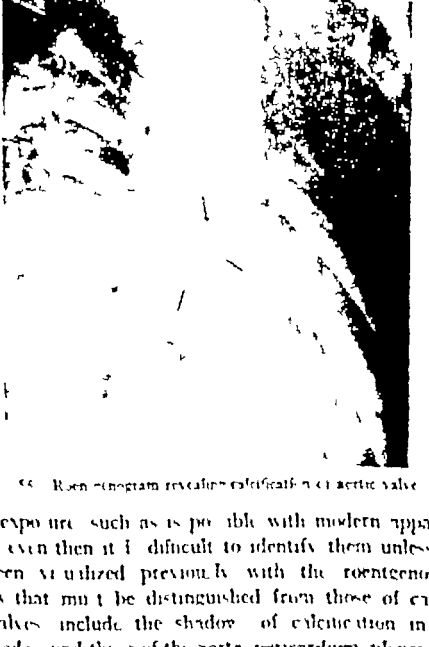

Fig. 88.—Roentgenogram revealing calcification of aortic valve

a rapid exposure such as is possible with modern apparatus is used, even then it is difficult to identify them unless they have been studied previously with the roentgenoscope Shadows that must be distinguished from those of calcified heart valves include the shadow of calcification in bronchial lymph nodes, and those of the aorta pericardium pleura lung and costal cartilages (Fig. 88)

In the fifteen cases which are considered, the presence of calcareous aortic stenosis was suspected clinically, and in each instance, roentgenoscopic evidence of calcification of the aortic valve was present When the roentgenologic changes that are associated with these cases and with others, which have gone to necropsy, are analyzed, certain variations in the distribution of the calcification are obvious These may be classified into three groups (1) calcification of the valves, (2) calcification of the annulus fibrosus, and (3) calcification of the valves or annulus fibrosus, or both, and of the contiguous myocardium The extent of the calcification varies a great deal, as the roentgenograms indicate

In reviewing some of the other roentgenologic features of these cases, it is interesting to note that ventricular hypertrophy was present in nearly all In those cases in which it was possible to estimate the degree of ventricular hypertrophy on a basis of four, seven were grade 2, one was grade 1, two were grade 3, and three were grade 4 Only 25 per cent of the patients revealed evidence of calcification of the aortic arch Tortuosity of the aorta does not seem to be a significant feature of this condition, since in the eleven cases in which it was recorded, seven revealed tortuosity of only grade 1, three of grade 2, and one of grade 3 The extent of calcification was not necessarily in keeping with the degree of hypertrophy or tortuosity of the aorta

Dr Willius has commented on four additional cases of calcification of the aortic valve, which were identified during routine roentgenoscopy for other conditions While these patients did not present roentgenologic evidence of calcareous aortic stenosis, they could not be distinguished from the cases belonging to that group

Dr Moersch How difficult is it to identify the shadow of this calcified valve with the fluoroscope? Dr Camp You have the motion of the calcified valves to help you We use an aperture about 2 inches square, and center over the situations of the valves, and if calcification is present, it is very easy to see There may be very little evidence of calcifica-

tion in a roentgenogram but the calcification may be very obvious fluoroscopically The dancing shadows of the calcified valves are so obvious that if one has seen such a case one should have no difficulty in recognizing others

Dr Keith Has subacute bacterial endocarditis developed in any of these 15 cases? Dr Willius No These cases have been observed during a period of only a year and a half

Dr Keith Do you not believe that the occurrence of subacute bacterial endocarditis in these cases should follow the same order as is implied by the theory that it occurs as a superimposed infection on a previously injured valve? Dr Willius Yes, except for the fact that these valves are so invaded with calcium that it seems incredible that any material blood supply to them can exist Thus, this status may be a protective mechanism against bacterial invasion

Dr Keith Would you place these calcareous lesions in the atherosclerotic group? Dr Willius No

Dr Keith I would like to ask one general question In our work on diffuse vascular disease three significant age periods occur The first comprises the young from infancy to the age of twenty five years regarding whom we have little knowledge, then the group between forty and fifty years in which capillary and arteriolar changes occur, and lastly, the older or arteriosclerotic group I am wondering whether this lesion you have discussed this morning falls in the middle age group Dr Willius The condition according to our material and to that of others tends to occur later than during the middle age period Then the occasional exception in the younger age periods is observed In this group one patient was twenty five years of age and one case occurred in the fourth, and one in the fifth decade of life

Dr Keith Then it occurs more frequently in the older age groups? Dr Willius Yes It is an insidious lesion which apparently has its origin early in life It permits the patient to live comfortably for many years and ultimately causes death beyond middle life This cycle of events strongly favors infection as an etiologic agent of the lesion

Dr Keith I would suggest studying the possible etiologic rôle of toxemia of pregnancy in these cases Dr Willius The fact that calcareous aortic stenosis predominantly affects males virtually eliminates this possibility

Dr Binger How many of these patients had hypertension? Dr Willius Only 2 of the 15 patients had hypertension

Dr Maytum Do you think that elderly patients who have a rough, aortic, systolic murmur, which suggests aortic sclerosis, should be sent for routine fluoroscopy to determine the condition of the valve leaflets? Dr Willius No I believe our efforts for the time being should be confined to those cases presenting the syndrome that I have described, and that Dr Camp should continue with his routine fluoroscopy of patients who already have been referred for roentgenography

Dr Keith How would you distinguish aortic sclerosis from calcareous aortic stenosis, without roentgenologic examination? Dr Willius In aortic sclerosis, the presence of a rough, aortic, systolic murmur is usually detected clinically In calcareous aortic stenosis the aortic systolic murmur is louder and rougher than the murmur of aortic sclerosis, and it is associated with a systolic thrill, absence of the aortic second sound, and cardiac enlargement

Dr Binger Did the four cases that Dr Camp accidentally discovered during routine fluoroscopy present symptoms and signs of heart disease? Dr Willius No One patient presented an aortic systolic murmur

Dr Keith Did any of these four patients have hypertension? Dr Willius One patient had hypertension

Dr Keith To me, it is the same old story that too much stress is placed on hypertension Patients have vascular disease which may or may not be associated with hypertension

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Medical Clinics of North America
September 1935 Mayo Clinic Number

ACUTE CORONARY OCCLUSION CLINICAL, ELECTRO-CARDIOGRAPHIC, AND NECROPSY FINDINGS IN TWO CASES

ARLIE R BARNES AND JAMES I WADE

REPORT OF CASES

Case I—A farmer aged fifty nine years came to the clinic complaining of "heart trouble" There was a history of "heart trouble" on both paternal and maternal sides of his family The patient gave a history of a systolic blood pressure of 165 mm of mercury but he could not remember the diastolic pressure The rest of the history was essentially negative He stated that for the last ten years he had noticed dyspnea on exertion and occasional "queer feelings" over the anterior part of his chest Two years before the dyspnea had become worse and substernal discomfort on exertion had developed Such discomfort lasting a few moments had subsided rapidly with rest and without medication He had been given digitalis at one time Three weeks before admission he had noted that he had anginal pain on any exertion This pain had been substernal in type and had extended into the left side of the neck and down both arms Rest had relieved the pain and no episodes of pain had lasted more than a brief interval Two weeks before admission he had awaked with severe pain under the lower portion of the sternum He had risen and walked about but the pain had persisted for the next four hours at which time the patient had called a physician He had been given some medicine for relief of his pain which gradually had subsided within the next eighteen hours In the course of the severe paroxysm of pain the patient had vomited twice He stated that December 30 two days before admission he had felt well when he had gone to bed but that substernal pain had appeared suddenly and had lasted almost all night His color was said to have been bad He had perspired freely and had been nauseated and had vomited several times The next morning the pain had persisted and he had called his physician who had advised him to enter the clinic

Examination revealed a slightly dyspneic man with a systolic blood pressure of 130 mm and a diastolic pressure of 90 mm The heart was enlarged to percussion the left border extending 1 cm from the midsternal line in the fifth intercostal space The rhythm was regular with a rate of the mitral second sound of 84 The apical systolic murmur was greater than the pulmonic second sound There were a few moist rales at the bases of both lungs The liver was not palpable and there was no edema of ankles There was bilateral inguinal adenopathy and the peripheral vessels were of

An electrocardiogram (Fig 59) disclosed a lengthened Q wave in lead III and inverted T waves in derivations II and III There was depression of the R T segment in derivation I and elevation and change of contour of the R-T segment in derivation III The Q and T patterns in the electrocardiogram were characteristic of acute infarction involving the posterior basal portion of the left ventricle Subsequent electrocardiograms have shown the same characteristics as those just described The patient's course has been uneventful while in the hospital

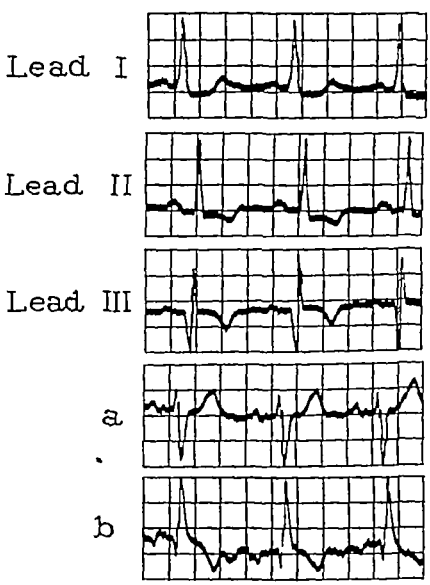


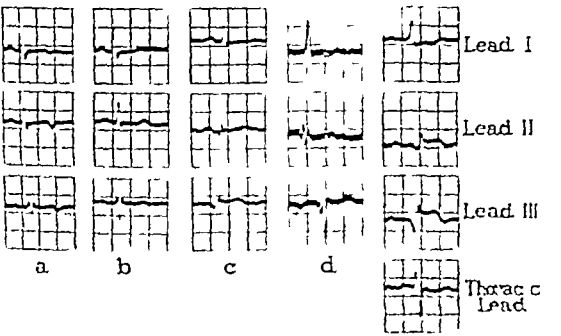
Fig 59.—Case I Standard electrocardiographic leads In addition the following are represented *a*, Electrocardiogram obtained by placing the right arm electrode on the posterior part of the chest and the left arm electrode on the chest wall in the precordial region *b*, Electrocardiogram obtained by applying the electrodes to the chest wall to obtain the fourth lead according to the method of Wood and Wolferth

Case II.—A white man, aged thirty-nine years, was first seen in the clinic in August, 1918 Subsequently he was reexamined eleven times The results of several of these examinations will be given here

In 1918, a diagnosis of latent syphilis was made, and the man was found to have, in addition, a blood pressure of 158 mm of mercury systolic and 98 diastolic, with mild changes in the retinal vessel characteristic of hypertension He was dismissed to follow antisyphilitic treatment He returned in April, 1923, when his blood pressure was found to be 170 mm of mercury systolic and 100 mm diastolic

In March, 1933, the patient was admitted to the hospital with the history that the previous December, while at rest, a dull, aching pain had developed in

the left anterior axillary line and had extended posteriorly to below the scapula This pain steadily had become worse had localized under the sternum and had lasted for twenty four hours He had been seen by a physician and had been given some pills for the relief of pain Shortly after this a similar attack of pain had occurred while the man was driving his car This attack had lasted for four hours and had been severe Following this second attack he had consulted a physician who had said that he had "heart trouble and had recommended that he spend three weeks in bed At the admission the patient was having typical seizures of angina pectoris on slight effort Two successive electrocardiograms showed that the T waves were inverted in all leads (Fig 60 a) For a period of three weeks the patient was given intramuscular in



had developed, and the patient stated that his temperature had risen to 100° F At examination in the clinic the blood pressure was found to be 170 mm of mercury systolic and 110 mm diastolic The retinal vessels were sclerosed and the heart was much enlarged The electrocardiogram, at this time, disclosed low amplitude of the QRS complex in lead II, a diphasic T wave in lead I with depression of the S-T segment in that lead, and elevation of the S-T segment in lead III (Fig 60, *c*) This electrocardiogram confirmed the definite impression gained from the history that the patient had had a second acute coronary occlusion in May, four months previously

At the last admission, December 17, 1934, he stated that he had felt well until a week previously, when he had noted that his heart had been beating fast, and that he had been dyspneic on the slightest exertion He had been following faithfully the dietary regimen, and had been taking digitalis under the observation of his physician Our examination revealed marked cardiac enlargement and auricular fibrillation An electrocardiogram was taken and revealed no significant change in the T waves or alteration in the RS-T complexes as compared to the previous tracing (Fig 60, *d*) His course for the next few days was uneventful, with the exception of troublesome hemorrhoids and some epigastric fullness which was found to be attributable to an enlarged left lobe of the liver December 26, nine days after admission, there was a severe seizure, with pain in the left shoulder and extending to the back and into the left axilla The pain was accompanied by nausea, a fall in blood pressure, moderate cyanosis, and signs of shock

Examination revealed that gallop rhythm had replaced fibrillation A friction rub was not audible but the heart sounds were of poor quality The electrocardiogram (Fig 60, *e*) was a characteristic T_3 type with depression of the S-T segment in lead I and elevation of the R-T segment in leads II and III The T waves were diphasic in all three leads The Q wave in lead III was prolonged, as was Q_3, although to a less extent, and the lowest amplitude of QRS occurred in lead II The thoracic lead showed a T wave of low voltage. Leukocytes numbered 15,000 per cubic millimeter of blood, and the temperature was normal The following day the patient was dyspneic, cyanosed, and failed rapidly

At necropsy the heart was found to weigh 658 gm The left coronary artery was sclerosed, grade 3 At a point 3 cm from its origin, the anterior descending branch was practically obliterated by calcareous intimal thickening Below this was a large area of healed, myocardial infarction This area involved the anterior portion of the left ventricle and a large portion of the adjacent interventricular septum The cardiac wall was markedly thinned in this area, which measured 4 by 6 cm The circumflex branch of the left coronary artery was sclerosed, grade 3

The right coronary artery was sclerosed grade 3 At a point 2 cm from its origin this vessel was occluded by a fresh thrombus which completely filled the lumen of the vessel, around to the point at which the vessel crossed the posterior interventricular septum There was acute myocardial infarction of the extreme basal portion of the posterior part of the left ventricle, of the interventricular septum, and of the adjacent portion of the right ventricle in an area measuring 2 by 4 cm Below the region of acute infarction in the

posterior basal portion of the left ventricle and posterior septum was an area of healed infarction which involved the mid posterior portion of the left ventricle and the adjacent interventricular septum There was thinning of the ventricular wall in this area which measured 3 by 4 cm

A thrombus 3 cm in diameter was present in the left auricle There were mural thrombi in both right and left ventricles

DISCUSSION

Dr Barnes Case I is a rather commonplace instance of infarction, but it has two or three interesting features

First of all, this patient's dyspnea had its onset at the age of fifty years, ten years before the onset of the anginal pain That is rather unusual It strikes me that most of these patients have little intimation of any cardiac embarrassment until the onset of the anginal syndrome It is evident that the cardiac insufficiency was attributable to inadequate coronary circulation

Another thing that is interesting about this case, a fact duplicated in many cases, is that the history suggests multiple infarcts This patient had an attack strongly suggesting acute coronary occlusion three weeks before coming to the clinic and another attack about a week before his admission It is possible that he had acute myocardial infarction to begin with and that later on there was extension of it There is histologic evidence to show that this occurs at times We must bear in mind the possibility of multiple infarcts because when we come to examine at necropsy such hearts as this patient had we often find two or three infarcts That fact complicates the electrocardiographic findings The areas of acute myocardial infarction may produce antagonistic electrocardiographic effects and thus may prevent the development of an electrocardiogram typical of acute coronary occlusion

The electrocardiogram of this patient is typical for the time after acute coronary occlusion at which it was obtained (Fig 59) First let us consider the initial ventricular complexes in the standard leads They constitute a fairly good Q pattern First of all a prolonged Q wave in lead III is present To be absolutely typical the Q wave should be fairly

well developed in lead II Another characteristic is the amplitude of the QRS complex It is usually smaller in lead II than in any other lead There is inversion of the T wave in leads II and III, and a rounding contour of the R-T segment in lead III and some depression of the S-T segment in lead I This is a characteristic T_3 type of electrocardiogram as seen in the third or fourth week after acute infarction and indicates that the infarction involves the posterior basal portion of the left ventricle

There is much interest now in the thoracic leads and particularly in the so-called "fourth lead" Wolferth and his associates have done splendid work on this subject To take the fourth lead, the right arm electrode is placed over the apex of the heart and the left arm electrode under the left scapula With this method we get normally an inverted T wave in lead IV A well-developed, initial, downward deflection is normally present In this case which we are presenting there is a normal fourth lead (Fig 59, *a* and *b*) The methods of applying the electrodes are given in the legend I am calling attention to this to show that lead IV is normal in this case of definite infarction, and that it is likely to be true in cases of posterior basal infarction As a matter of fact, in Wolferth's publication he has only one tracing in which lead IV of his type B was as definitely characteristic of infarction as were the three standard leads

Recovery of the patient of Case I was uneventful, and the prognosis is relatively good The question has been raised as to whether or not the prognosis is better in cases of posterior basal than of anterior infarction of the left ventricle Wolferth has expressed the belief that it is better in the former I agree with him insofar as the immediate attack is concerned The patient's liability to subsequent acute coronary occlusion, which is the great danger, is approximately as great if the individual has had a posterior infarct as it is if he has had an anterior infarction An infarction, no matter what vessel is involved, implies that there may be another, with probable fatal result

Question Is the effect on the electrocardiogram in occlusion attributable to the absence of action in the infarcted portion or to the excessive action of the rest of the heart?

Dr Barnes This question cannot be answered with certainty It is highly probable that disturbances of electrical potential produced by injured muscle play an important part in the early electrocardiographic changes There is a strong probability that the activation time in the area of infarction is abnormal This might account for persistence of electrocardiographic changes of myocardial infarction long after the remnants of muscle in that area could be said to be dying

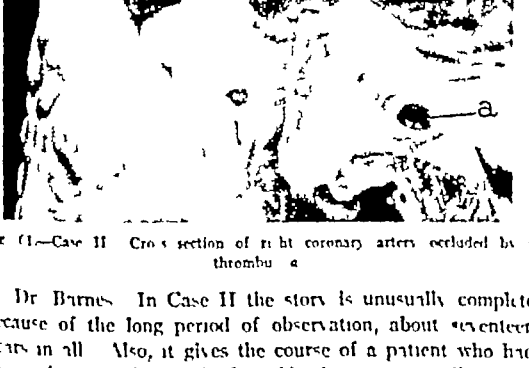


Fig 61—Case II Cross section of right coronary artery occluded by a thrombus a

Dr Barnes In Case II the story is unusually complete because of the long period of observation, about seventeen years in all Also, it gives the course of a patient who had benign hypertension and whose blood pressure readings had been high for a long time As much as seven years ago the patient had a diastolic pressure of 120 mm of mercury In spite of the hypertension he had been well until coronary disease had supervened I saw the patient in March 1933 There was definite evidence that he had had coronary occlusion preceding his admission to the clinic at that time I saw him in September of the same year and again there was

definite evidence of occlusion in the preceding month of May Finally, there was the attack of occlusion which had caused the patient's death

We have some illustrations which will illustrate the chief points of interest in the heart at necropsy in Case II Figure 61 is a cross section of the right coronary artery occluded by a thrombus Figure 62 represents the left ventricle, which is markedly dilated It is possible to see the region in which

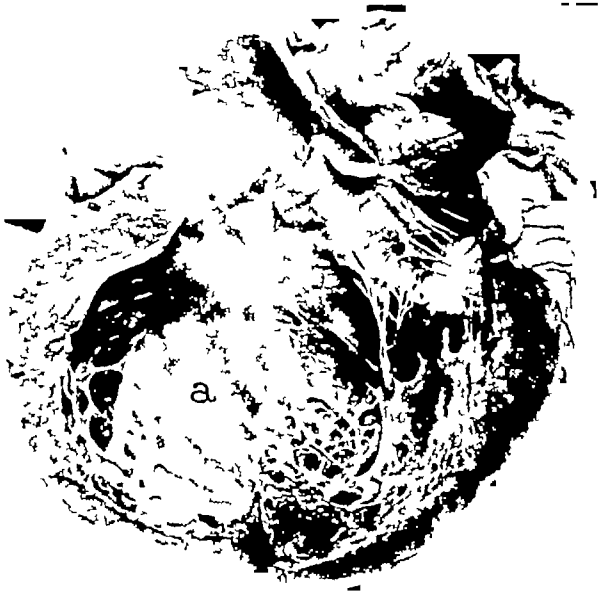


Fig 62 —Heart showing large area of endocardial fibrosis at the site *a* of the previous acute myocardial infarction involving the anterior apical portion of the left ventricle and the adjacent interventricular septum

sclerosis has taken place, replacing the large anterior apical and septal infarct (Fig 63) If a portion of the muscle were cut away farther back a rather large area of old infarction would be revealed, with thinning of the posterior wall of the left ventricle and atrophy of the posterior papillary muscle Still farther back, and close to the base of the left ventricle, would be found an acute infarct involving an adjacent part of the septum, and most interestingly, a large area in the ad-

jacent portion of the right ventricle An infarct in the right ventricle is very rare, and this is one of the few we have seen This extensive infarction of the right ventricle can be accounted for by the situation and extent of the thrombus that occupied the lumen of the right coronary artery Figure 63 is simply a tangential section to show the fibrosis that has occurred in the region of chronic infarction The descending aorta and iliac branches show an extreme degree of senile sclerosis (Fig 64)

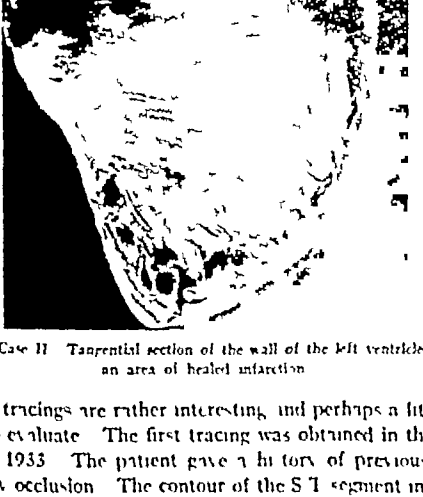


Fig 63 — Case II Tangential section of the wall of the left ventricle showing an area of healed infarction

The tracings are rather interesting and perhaps a little difficult to evaluate The first tracing was obtained in the early part of 1933 The patient gave a history of previous acute coronary occlusion The contour of the S-T segment in lead I suggests that the patient has had a previous infarction in the anterior and apical portion of the left ventricle (Fig 60 a) If the T wave in lead I were attributable to hypertension it would be expected that the S-T segment would be depressed but it is not The electrocardiogram was repeated and in

identical tracing was obtained At this time the patient could not walk more than two or three blocks without anginal pain A muscle extract (myoston) was then administered for three weeks There was marked improvement in the patient's tolerance to exercise He was able to walk six blocks without pain

Fig 64 —Case II Senile sclerosis in the descending aorta and iliac arteries

He was sleeping better and his general condition was better At the end of that time the T wave was upright in all leads (Fig 60, *b*) I was inclined to feel that a remarkable result had been achieved, because the electrocardiogram does not change easily Later I felt that possibly the electrocardio-

gram was returning spontaneously to normal after coronary occlusion and that myoston had hastened the process That return to normal was quicker than anything I have seen in these cases I think that, along with the clinical improvement, the muscle extract did something that definitely hastened the return to normal I said a moment ago that the occurrence of one acute coronary occlusion is a signal that the patient may have another

The patient came back in September At that time he gave a definite history of acute coronary occlusion in the preceding May The electrocardiogram has changed to a type suggesting that the recent infarct has involved the posterior portion of the left ventricle (Fig 60 *c*) A marked Q_3 is present The amplitude of the QRS complex in lead II is less than in any other lead The R T segment in lead III is elevated To be sure that this tracing was indicative of infarction of the posterior portion of the left ventricle we should have inverted T waves in leads II and III, with the R T segments preceding them arising on or about the iso-electric line The next tracing is one we obtained on the patient's last visit to the clinic, the last part of 1934 (Fig 60, *d*) Now we have an electrocardiogram that is characteristic of hypertension There is a diphasic T wave in lead I with low take-off of the S-T segment in that lead The patient was under observation in the hospital and the next electrocardiogram was taken just a few hours after an attack of acute coronary occlusion (Fig 60, *e*) This is a typical electrocardiogram of acute myocardial infarction The T_3 pattern present here is characterized by elevation of the R T segments in leads II and III and a depressed S T segment in lead I The Q_3 pattern is also present The thoracic lead (Fig 60 *e*) reproduced here was taken with the electrodes applied to the thoracic wall exactly opposite to the method described for the fourth lead by Wolferth This thoracic lead yields a normal tracing in this case except for low voltage of the T wave

This patient illustrates the amount of injury that a heart may be able to withstand This man had two large cardiac

infarctions which he survived, in the face of the fact that he had hypertensive disease, finally succumbing to a third massive acute myocardial infarct

Question What effect do you attribute to tissue extract? Dr Barnes It appeared to produce marked improvement in the anginal syndrome in this case, in the beginning I assumed at the time that this was the result of improved coronary circulation Subsequent investigations have thrown doubt on such an assumption Of course it is difficult to separate fancy from fact

Question Did you observe an increase in the minute volume of the heart following the giving of muscle extract? It has been thought that the extract increased the amount of one of the constituents concerned in muscle metabolism, that it acts something like a catalyst, and if that is the case we might expect a stronger contraction which ought to give an increased volume and might also raise the blood pressure Dr Barnes The muscle extract brought no rise in blood pressure I have not seen a report of an actual study of the volume output with the extract It may be that its action is essentially catalytic I do not know how firmly that has been established

Question Do you find any pentnucleotide being used? It is used in agranulocytosis but I do not know whether it is used here Dr Barnes I do not know of anyone using pentnucleotide in the treatment of angina pectoris

Question What is the greatest number of attacks that a patient with coronary occlusion has had before he has succumbed? Dr Barnes We have a man in the city here who has had three definite attacks of acute coronary occlusion from which he has recovered He is still alive, four years after the last attack I think that is our best case

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AURICULAR FIBRILLATION MECHANISM, SIGNIFICANCE, INCIDENCE AND TREATMENT

HARRY L. SMITH

I have been requested as my contribution to this Clinical Week, to talk on a subject with which I know all of you are familiar. Auricular fibrillation has been, and continues to be, the most frequent of the significant forms of cardiac irregularity. From a clinical standpoint there are two main types of auricular fibrillation: the intermittent type and the continuous, permanent or chronic type. The intermittent type may occur in paroxysms or in transient periods that last from a few minutes to several days.

MECHANISM

In auricular fibrillation the auricles no longer contract. The walls are dilated in a state of diastole and are undergoing very rapid, incoordinated, fibrillary twitchings. The auricles lose their pump like action and they act only as reservoirs. There are several theories advanced to explain this irregularity, but the two most commonly quoted are the circus movement described by Lewis and the German theory. The circus movement is present in both auricular fibrillation and auricular flutter. In auricular fibrillation the paths of conduction are not always the same. There is an increase in the rate of contraction of a central ring, and a shortening of duration of contraction of the individual muscle fibers. This causes variation in the paths by which contractions spread from the central ring to the outlying parts of the auricular wall.

The stimuli that are responsible for auricular fibrillation are extremely rapid. They vary from 450 to 1000 per minute. The German theory is that the auricular fibrillation is attrib-

utable to multiple foci of impulse formation in the auricular walls Whether auricular fibrillation is attributable to the circus movement, or to multiple foci of formation of impulses has very little practical importance as far as diagnosis, treatment, and prognosis are concerned The impulses that are responsible for auricular fibrillation do not arise at the sino-auricular node Owing to the extremely rapid, inadequate production of the stimuli, only a few of these impulses are conducted through the auriculoventricular bundle This results in a very irregular ventricular action, and when the ventricular rate is very rapid, ventricular action often is ineffectual That is, the ventricles are incapable of opening the aortic cusps This produces a difference in the rate of the apex pulse and of the radial pulse, which is known as pulse deficit

DIAGNOSIS

In the majority of instances the diagnosis of auricular fibrillation is not difficult The condition usually can be diagnosed by listening to the heart with a stethoscope It is more difficult to diagnose if the auricular fibrillation is very slow The irregularity is a total irregularity or an irregular irregularity There is something about auricular fibrillation which is characteristic of this particular type of arrhythmia, that is, there are peculiar, characteristic, little runs of irregularity This is a characteristic which I often rely on in making this diagnosis The rate is variable The usual rate is often given as from 110 to 160 per minute, although the rate may be much slower than this, and at times faster In some instances the diagnosis has to be made by the aid of the electrocardiogram The characteristics of the electrocardiogram of a patient whose auricles are fibrillating are as follows 1 No two cycles of the electrocardiogram are of equal length 2 There are frequent variations in the amplitude of the R wave 3 The P wave is entirely absent, and small, irregular wavelets often are present At first glance these wavelets appear to be of the same amplitude, but if the wavelets are measured it will be found that they vary in height, width and rate

ETIOLOGY AND INCIDENCE

In our experience at the clinic, the most common cause of auricular fibrillation is hypertensive and coronary heart disease, occurring singly or combined. The incidence of auricular fibrillation in the combined condition of hypertensive coronary heart disease, in a series of 1,045 cases studied, was 33.9 per cent. Hyperthyroidism occurred second in frequency, with 32 per cent. Chronic mitral endocarditis, with mitral stenosis and insufficiency, occurred third in frequency, with a percentage of 22.

In another series, I examined records of 100 cases of chronic rheumatic endocarditis with mitral stenosis, and in that group there were twenty cases of auricular fibrillation, or an incidence of 20 per cent. Auricular fibrillation will vary considerably in the presence of mitral stenosis, depending on the duration, degree, or the severity of the mitral stenosis present. The next group studied consisted of 205 cases of adenomatous goiter with hyperthyroidism. In this series there were twenty nine cases of auricular fibrillation, or an incidence of 14 per cent. Another group was that of chronic adhesive pericarditis. There were 144 cases with eighteen cases of auricular fibrillation or 12 per cent. This group of cases of pericarditis should not be compared with other groups mentioned here, because in all of the cases of adhesive pericarditis necropsy was performed, whereas, in the other groups necropsy was performed in only a small percentage of cases. The next group studied was 100 cases of aortic stenosis; there were eight cases of auricular fibrillation or an incidence of 8 per cent. Exophthalmic goiter was next, with ten cases of auricular fibrillation in a series of 203 cases of exophthalmic goiter or an incidence of 4.9 per cent. In 100 cases of rheumatic aortic insufficiency, there were four cases of auricular fibrillation or an incidence of 4 per cent. In 100 cases of syphilitic aortitis there were four cases of auricular fibrillation, or an incidence of 4 per cent, and in 100 cases of hypertensive heart disease there were four cases of auricular fibrillation, an incidence of 4 per cent. In a group of 113 cases of

pericarditis with effusion there were four instances of auricular fibrillation, a percentage of 3 5 In 100 cases of coronary sclerosis without hypertension there were three instances of auricular fibrillation, in 100 cases of congenital heart disease there were two cases of auricular fibrillation, and in 100 cases of subacute bacterial endocarditis there was one instance of auricular fibrillation Auricular fibrillation is very rare in subacute bacterial endocarditis Just why this should be so is not entirely understood

In another study,[2] which Magee and I made to ascertain the influence of age on auricular fibrillation and hyperthyroidism, we found that among patients who were subjected to the effects of hyperthyroidism, old hearts were prone to fibrillate and young hearts to maintain normal rhythm The increased incidence of auricular fibrillation in hyperthyroidism which occurs after middle life can be attributed only in part to hypertension and arteriosclerosis with their attendant cardiac lesions Although associated in a minority of cases with definite cardiac injury, cardiac hypertrophy, and occasionally marked congestive heart failure, auricular fibrillation and hyperthyroidism are usually not accompanied by serious or permanent injury to the heart In hearts injured by hyperthyroidism or by a combination of hyperthyroidism and intrinsic heart disease, auricular fibrillation is frequently prolonged and may persist permanently, but tends to give place spontaneously to normal rhythm when the heart has been relieved of the effects of hyperthyroidism When serious cardiac injury has not occurred, auricular fibrillation is more often intermittent and transient The arrhythmia very frequently develops for the first time during the immediate postoperative period, in which case it ceases spontaneously in a few hours to a few days Auricular fibrillation occurs more frequently in hyperfunctioning adenomatous goiter than in exophthalmic goiter The longer duration of hyperthyroidism in adenomatous goiter, and the fact that usually adenomatous goiter occurs among people who are about ten years older than those who have exophthalmic goiter, partially account for the greater inci-

dence of auricular fibrillation in the presence of the former disease.

TREATMENT

The treatment of auricular fibrillation primarily depends on the cause, the type, and the degree of the associated heart disease present In most instances, intermittent auricular fibrillation may not need any treatment If auricular fibrillation is of short duration and there is little evidence of any serious cardiac lesion, it may be well to establish normal rhythm by administration of tincture of digitalis or quinidine Quinidine is more efficacious in the establishment of normal rhythm in auricular fibrillation than is digitalis When auricular fibrillation is associated with serious cardiac injury, as a rule I believe it is unwise to try to establish normal rhythm in the majority of instances What I try to do with medication is to slow the rate rather than to establish normal rhythm

The prognosis, of course, depends on the associated cardiac lesion present

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ESSENTIAL HYPERTENSION

GEORGE E. BROWN

I do not know of any condition that is more aggravating than hypertension. During the last three years at the clinic we have attempted to concentrate some activity in this field, our interest in this subject has been increased by the developments in the field of surgery of the sympathetic nervous system. What I am going to talk about this afternoon is not altogether fact, there are some facts, some hypotheses, and some theories, but altogether they comprise a concept that is rather interesting at the moment. First, I think, it is a good idea to define what I am attempting to talk about. Essential hypertension is a definite thing. I know nothing about its cause. If an attempt was made to take 100 patients who had high blood pressure, and who came to the clinic and to place them in definite categories according to their blood pressure, it would be found that about 98 per cent would be classified as having essential hypertension and that 2 per cent would be classified as having secondary hypertension. Some diseases which affect the blood pressure secondarily are coarctation of the aorta, aortic heart disease, exophthalmic goiter and other conditions which cause hyperthyroidism, glomerulonephritis and paroxysmal hypertension. As time goes on more cases will be taken from the group we have called essential hypertension and will be classified definitely. However little is known about the etiology of essential hypertension.

If there is anything that is known about essential hypertension it is that it is common among members of some families. All physicians have seen this. The statistics of the familial incidence have varied, of course, according to the in-

vestigator In about 50 per cent of the cases of essential hypertension which have been seen at the clinic, it has been possible to determine from the family history that the father or mother of the patient also had hypertension Weisman, whose figures are the highest, said that about 69 per cent of the patients who have essential hypertension give a family history of this condition The more this factor is investi gated, the more accurate and certain it remains Essential hypertension is a familial characteristic of an individual The second point is, if it is a familial condition, what is it? What do we inherit when we have high blood pressure?

An interesting piece of work has been done in this connec tion on the vasomotor mechanism in cases of high blood pres sure If individuals who have any degree of hypertension are stimulated in any way, either emotionally through a sensory stimulus such as cold, or by other types of stimuli, they react with an excessive response of the blood pressure If normal persons, or persons who have any other disease, are stimulated in the same manner, there is much less marked response Therefore, it has been found that the characteristic abnormality in high blood pres sure is an over-reaction of the blood pressure to stimula tion A very simple test has been devised to determine this reactibility The hand of the patient is placed in ice water, at 4° to 5° C (39 2° to 41° F), and the arm is immersed A strong, sensory thermal stimulus will be produced and the blood pressure will rise sharply This test has been carried out in other types of disease, and I never have seen any other disease effect this type of response Normal persons have an increase of approximately 11 mm of mercury in systolic pres sure after this stimulation The highest value is tentatively set at 22 mm of mercury The average increase is about 11 mm for the systolic and 9 mm for the diastolic pressures, respectively Patients who have definite clinical hypertension respond with an increase of from 30 to 100 mm of mercury A normal person does not respond to the same degree, in other words, the vasomotor reactions of patients who have hyper-

tension is exaggerated There were some 'normal" individuals who had normal blood pressures and yet had a hypertensive response to this stimulation This of course was a rather surprising finding It may fill in the gap of knowledge as to when hypertension starts The families of these hyper reac tive normal subjects were investigated and about 85 per cent of the subjects gave histories which revealed that the fathers or mothers had high blood pressure At this point the hypoth esis is advanced that these individuals are those who are going to have high blood pressure Dr Hines has gone to the schools and has examined a large number of students to de termine the percentage incidence of over reactive mechanisms and in the cases of children who had this over reactive mech anism he investigated the blood pressures of their relatives

Dr Hines These studies, which were carried out among students in school are not complete I have carried out the cold test in about 250 cases The ages of the subjects ranged between six and nineteen years I have studied those students whose blood pressure rose more than 20 mm of mercury after the stimulation Fifteen per cent of these 250 students, so far, have given this abnormal pressor reaction In order to get more information about the hereditary factor, I have at tempted to follow family groups, and particularly those from which I could get families of two, three or four generations This has been a very difficult problem because in this country it is difficult to find large families of more than one or two generations, who are living in one section of the country I have found about twelve such families here and I have done the cold test on every living member There is one family in which there are six children two have hyperten ion and three of the remaining four give a hypertensive type of reac tion to the cold test The second family is a normal one in which there is no known evidence of hyperten ion The grand parents died of old age The parents gave normal reactions to the cold test and their blood pressures were normal Six children also were tested and all were normal In the third family there was high blood pressure on one side of the family

and normal blood pressure on the other side Except for one member, who died of hypertension at the age of forty-six years, all have had their blood pressures taken and have been subjected to the cold test Hypertension is present in one side of the family and three of the five children disclosed an abnormal reaction to the cold test This demonstrates that hypertension is a dominant characteristic In another very interesting family, which I have been fortunate in locating, there are thirty-nine grandchildren The grandparents are still living Normal blood pressures and normal vasomotor reactions run throughout one side of the family, and hypertension runs throughout the other side of the family As I said before, these studies have not been completed, but the individuals who have been tested so far certainly indicate that there is constitutional predisposition to the abnormal vaso motor reaction Certain families react only slightly to the cold test and the members of other families reveal severe reactions Studies seem to indicate that the more severe reactions occur in cases in which the patients have a hypertensive diathesis

Dr Brown Although it is not an established fact, I think it is safe to advance the conception that essential hypertension means the inheritance of a vasomotor mechanism that reacts excessively to its inner and external environment The mechanism is not known All of the autonomic functions of the body are not based on an exact level and normality There are variations Some people have normal temperatures and some have temperatures which are subnormal but which are normal for them Miss Roth and Dr Hargraves have been working on other angles of this problem and their purpose has been to obtain information as to whether this abnormality of the vasomotor mechanism of hypertensive subjects is central or peripheral We do not know whether the vasomotor center is hyper-reactive or whether the suprarenal glands produce too much epinephrine, but the problem has been to set up an experiment that would give us some information as to whether the central or peripheral mechanism was involved Carbon

dioxide is a stimulant to the cerebral centers That is why it has been used as a respiratory stimulant Therefore, individuals who had hypertension were allowed to inhale carbon dioxide of a concentration of 10 per cent in oxygen Miss Roth and Dr Hargraves found that the increases in blood pressure were two to three times those obtained in subjects with low blood pressure The information which they have obtained is confirmation that there is hypothetically a vasomotor center in the medulla, which reacts excessively to stimulation, and that the stimulus acts only on the centers of the brain It is confirmation of the probability of a central origin of the abnormal reaction I believe the hypertensive subject is born with an abnormally reacting vasomotor center, which reacts excessively throughout life This may be the primary agent in the production of hypertension in later years of life Clinical hypertension develops in these individuals when the systolic and diastolic pressures are above normal Arterioles in the body become narrowed, as is shown by their appearance in the retinæ Up to this time, these individuals have been "carriers" of the hypertensive condition If it were possible to isolate the individual before blood pressure was definitely increased, the age at which clinical hypertension would develop would theoretically be delayed But with the stress and strain of modern life, the levels of blood pressure usually begin to increase, perhaps in the fourth or fifth decade of life At this time the condition has an organic basis

There is a form of hypertension which is of great interest This is the so-called latent hypertension in which there are pathologic changes demonstrable in arterioles and normal or subnormal levels of blood pressure Cold is carried out on these patients reveal marked rises in blood pressures These people probably go through life until later years with hyperreactive blood pressures arteriolar narrowing develop before clinical hypertension is evident The excessive reaction may be the cause of the vascular changes If the cause of the subemergence were known it perhaps would furnish the answer to the problem of the control of hypertension

All of this leads up to the question of what can be done about this disease Patients have to be treated At the pres ent moment there are two viewpoints The first is that if the hypertension is recognized at birth or puberty, the environ mental influences could be controlled in some degree and the hypertension might be kept submerged for a long time The second viewpoint is that if these excessive reactions are the important part of hypertension, some approach should be made to the problem whereby these reactions could be di minished

If from the muscles of a normal person is taken an arteriole of a diameter of approximately 100 microns, the lumen will be found to be approximately twice the thickness of the wall In advanced cases of hypertension the diameter of the lumen approaches the thickness of the wall The importance of this is that in all considerations of treatment of hypertension, the fact of irreversible organic change must be kept in mind One cannot expect the impossible This furnishes some basis for estimating the improvement which can be obtained from operative procedures in cases of hypertension

The surgical treatment of hypertension has been ap proached in three ways It has been discovered that after removal of the sympathetic ganglions, the peripheral blood vessels become dilated and remain dilated Sympathectomy was first applied to hypertension by an Italian, named Pierri, who resected the splanchnic nerves He reported two cases, without details of effects on blood pressure Dr Craig has carried out a series of bilateral or unilateral splanchnic operations Three of the six patients obtained sufficient improvement to make the operation worth while The second surgical approach was by operation on suprarenal glands Essential hypertension, it was thought, might be helped by subtotal suprarenalectomy, that is, removal of one suprarenal gland and of part of the other Our experience at the clinic has been rather limited We have under observation one patient who throws light on this problem The patient has high blood pressure, changes in her appearance that would suggest

a cortical tumor of the suprarenal glands, gradual development of obesity, amenorrhea, and some weakness An exploratory operation was performed but nothing abnormal was found in the glands Dr Walters removed one suprarenal gland and approximately 60 per cent of the other Mild suprarenal insufficiency is now developing She still has marked hypertension even with this decrease in the supply of epinephrine The third phase of surgical treatment is what is of particular interest to us now Dr Adson, in attempting to relieve the pains of gastric crises, resected the anterior motor and posterior roots from the fifth thoracic, to and including the second lumbar nerves Sharp changes were observed in the blood pressure with changes in posture This gave us an idea that loss of splanchnic control of the arteries had effected a fall in blood pressure On the basis of this finding, Adson and Craig have carried out sixteen operations for relief of various forms of severe essential hypertension Anterior rhizotomy has been done in all of these cases What is accomplished by this operation? The sympathetic fibers leave the cord by way of the anterior motor roots Complete denervation of the splanchnic bed is effected by cutting these roots Sweating disappears below the level of the umbilicus The feet become hot and the abdominal wall is paralyzed This diminishes intra abdominal tension and is one of the factors in lowering blood pressure from posture In cases in which there were changes in retinal vessels indicating malignant forms of hypertension the blood pressure has become sharply reduced during the period of observation up to three months The first patient was operated on four years ago The retinitis cleared up, and the systolic blood pressure is averaging 170 mm of mercury and the diastolic 100 mm and the condition has been converted from a severe to a very mild form of hypertension I do not think that this represents a cure for high blood pressure

Five years would be the shortest time in which it would be possible to tell what we have done for these people We know that we have not injured them other than that we have

paralyzed the abdominal wall From this there has been no important disability, and it has been a factor in lowering the blood pressure For the first time, it is possible significantly to modify blood pressure For how long this will endure, time will tell Essential hypertension is a great deal like Raynaud's disease Raynaud's disease is a vasomotor hyperactivity exerting its major effects on the vessels of the skin By cutting of the vasomotor fibers, it is possible to control the condition but the cause is still unknown This is the present status of our studies on high blood pressure There is some reason to hope that as time goes on more light will be thrown on the subject and that the facts ultimately will be known

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MEDICAL ASPECTS OF CONGENITAL ARTERIOVENOUS FISTULA, REPORT OF A CASE INVOLVING THE LOWER EXTREMITY

BAYARD T HORTON

I wish to present this case of congenital arteriovenous fistula to call attention to the common clinical signs and symptoms that are produced by such a vascular anomaly Congenital arteriovenous fistula occurs more often in the extremities than in other parts of the body It is a condition which probably is often seen but seldom recognized by the general practicing physician and surgeon The truth of this statement, I believe is borne out by the fact that since June 28, 1929, I have studied forty cases of congenital arteriovenous fistula of the extremities, and yet in only one of these had the condition been diagnosed prior to the patient s admission to the clinic If a physician has ever seen a typical case of this type and fully appreciates the entire clinical picture he is not likely to fail to diagnose the next case that comes under his observation I use the term arteriovenous fistula to designate any abnormal communication between an artery and a vein by means of which arterial blood passes from an artery to a vein without passing through a capillary bed The terms cirsoid aneurysm arteriovenous aneurysm pulsating venous aneurysm arteriovenous varix serpentine aneurysm plexiform angioma angioma arteriale racemosum and angioma arteriale serpiginosum appear in the literature but these terms are merely descriptive of superficial manifestations of a single underlying condition arteriovenous fistula The fundamental condition is the same and the resulting processes in the vascular system are similar regardless of the location of the fistula

The general appearance of the involved extremity in this series of forty patients who had congenital arteriovenous fistulas has been markedly similar The involved extremity exhibited marked evidence of engorgement, and in more than 50 per cent of the cases in which the lower extremities were involved, ulcers were present in the foot or lower third of the leg Some of the superficial veins were enlarged and dilated to a marked degree This results from the fact that arterial blood under arterial pressure is shunted by way of the arterio venous fistula into the thin-walled veins, and causes them to dilate and form aneurysmal sacs The circumference of the abnormal extremity was from 2 to 8 cm greater than that of the corresponding normal extremity, and there was an increase of from 0 5 to 7 cm in the length of the bones of the abnormal extremity over the length of the bones of the normal extremity The basis of abnormal growth of bone is not entirely clear An excessive amount of blood is present in the limb and this may produce or stimulate overgrowth

The following case illustrates the usual clinical signs and symptoms that are observed in congenital arteriovenous fistula of the lower extremities, except for the absence of a bruit and thrill

REPORT OF CASE

A girl, aged nineteen years, came to the clinic October 7, 1930, because of an ulcer about the right internal malleolus, which had been present since she was nine years of age Five years before, she first had noted that the right leg was longer than the left, and that the superficial veins were more prominent on the right leg than they were on the left Four years before, the ulcer remained healed for three months, but this was the only time that it had disclosed any tendency toward healing She had never received an injury which would account for the ulcer Her general health had always been excellent. She had had scarlatina in childhood, but had not had any other infectious diseases The diagnosis of "varicose ulcer" had been made by numerous physicians elsewhere, and the ulcer had been treated with salves of various types Several physicians had thought that the ulcer was tuberculous She had received several applications of roentgenotherapy in 1924, 1925, and 1928, but these had served only to aggravate the condition

There was a small, crusted ulcer (Fig 65) in the region of the right internal malleolus and adjacent to the ulcer were numerous papular, purple, telangiectatic lesions A similar lesion involved the second right toe (Fig 66) No definite pain was associated with these lesions The general physical exam

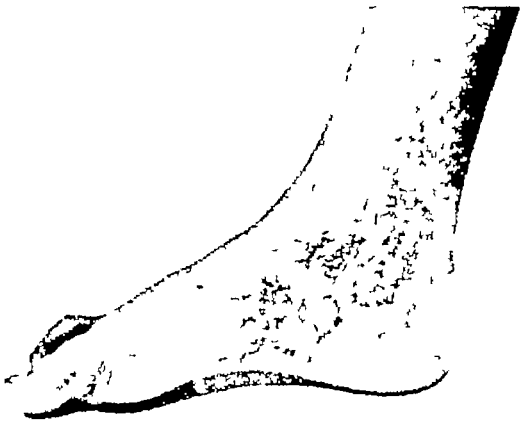

FIG. 65.—Inner aspect of right foot trophic changes and formation of ulcer present October 1930

FIG. 66.—Anterior view of right foot the toes showing to record toe may be

mation revealed cardiac hypertrophy, graded 1, lateral curvature of the spine, and the condition in the right leg The right leg measured 42.5 cm from the patella to the internal malleolus, and the left leg measured 40 cm (Fig 67) The right and left femurs were the same length The right foot was slightly larger than the left Surface temperatures that were taken by means of the electric thermocouple at corresponding areas and on both feet and legs re

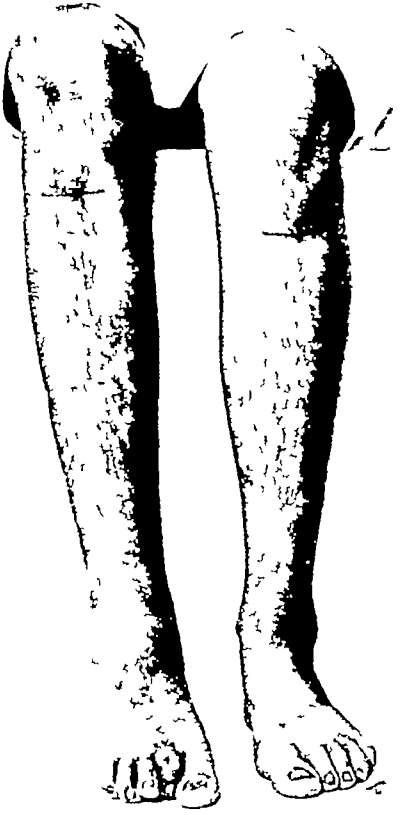

Fig 67 —Anterior view of both legs, increase in length and size of right leg may be noted

vealed that the right leg was from 2° to 3° C warmer than the left leg The temperature over the ulcer in the region of the right internal malleolus, was 33 4° C (92 1° F) while that of the corresponding area on the left internal malleolus was 31 9° C (89 4° F) The temperature of the toes of the right foot ranged from 32 6° to 33.8° C (90 7° to 92.8° F) That of the left foot was 32° C (89 6° F) No thrill or bruit could be detected in the right leg or

foot. The right foot liberated 57 small calories of heat and the left liberated 1 small calories.

The studies of the oxygen content may be noted in Table 1 Blood that was obtained from a superficial vein near the right ankle was bright red and appeared like arterial blood The oxygen saturation was 96 7 per cent Blood that was obtained from a superficial vein of the right arm was dark red and had an oxygen saturation of 83 per cent. The patient was lying in a horizontal position, and had been at rest for about thirty minutes before withdrawal of the blood. The blood was collected in a small tube under oil and was withdrawn without the use of a tourniquet The oxygen content and capacity were determined by the gasometric method of Van Slyke

When the right femoral artery was compressed by digital pressure below Poupart's ligament the apex beat of the heart decreased 10 beats (from 84 to 4) per minute No change was observed when the left femoral artery was compressed in a similar manner

The blood pressure in the right arm was 136 mm of mercury systolic and 85 mm of mercury diastolic In the left arm the systolic pressure was 128 mm of mercury and the diastolic pressure 8 mm of mercury Urinalysis revealed

TABLE 1

OXYGEN STUDIES I CASE OF CONGENITAL ARTERIOVENOUS FISTULA

Blood.	Oxygen capacity volumes per cent.	Oxygen content volumes per cent	Oxygen saturation, per cent
Right arm vein	17 59	14 6	83 0
Right leg vein	17 53	17 02	96 7

was applied in a spiral manner from the arch of the foot to the knee. It was hoped that the pressure which was exerted by the bandage would decrease the flow of blood through the fistula, and cause more blood to flow through the capillary bed in the foot and leg

The patient was dismissed October 29, 1930, and in a letter, which was received December 8, 1930, she stated that the ulcer had entirely healed, and that the foot looked well (Fig 68) She has continued to wear the bandage, and says that she is unable to get along without it In a letter, which was

Fig 68—Inner aspect of right foot and leg December 8, 1930 The ulcer and trophic changes illustrated in Fig 65 have completely healed The spiral creases were produced by the rubber bandage The photograph had been taken immediately after the bandage was removed

received April 6, 1934, she said that the right leg feels well and that she has had no recurrence of the ulcer This type of treatment is only palliative, but may be sufficient to prevent additional trophic changes in the right leg, and to decrease the work of the heart

COMMENT

The important points to remember in the diagnosis of congenital arteriovenous fistulas of the extremities are (1) in-

creased length and size of the extremity (2) increased surface temperature and elimination of heat and (3) demonstration of a large portion of arterial blood in the regional veins The bradycardia is confirmatory evidence, but is often absent if the fistulas are small The finding of arterial blood in the regional veins is diagnostic of an arteriovenous fistula This is a test which was introduced originally by Dr G E Brown

Dr Brown This represents a typical case of congenital arteriovenous fistula of the lower extremity and with the exception of a bruit and thrill all of the classical signs and symptoms, which are associated with such a vascular anomaly, are represented in this case I agree with Dr Horton that if a physician fully appreciates the entire clinical picture which has just been presented, he should have no difficulty in recognizing the next case which he sees

Visiting physician Dr Horton, you mention that in these cases of congenital arteriovenous fistula there is an excess of blood in the involved extremity as noted by an increase in the surface temperature and in the elimination of heat How do you explain the presence of gangrene and formation of ulcer in the presence of so much blood? Dr Horton Trophic changes, ulcers, and even gangrene develop because the arterial blood is shunted by way of the abnormal arteriovenous communications directly into the veins and the blood for the most part, does not pass through the normal capillary bed For that reason there is a relative degree of anoxemia in the area or areas in which the blood fails to pass through the normal capillary bed Hence the development of trophic changes, formation of ulcer, and gangrene Oxygen exchange from the blood stream to the tissues takes place only through the capillary bed, and not through the walls of the larger vessels

Visiting physician Why is it that the trophic changes come relatively late in life of patients who have congenital arteriovenous fistula? Dr Horton Trophic changes I believe are observed, on the average by the fifteenth or eighteenth year A great deal depends on the size of the abnormal

arteriovenous communications If these communications are large and a large amount of blood is shunted into the veins, the trophic changes occur early in life, but if the communications are small and only a small amount of blood is short circuited into the veins, trophic changes may occur late in life, at least once I have seen this delayed until the patient was approximately sixty years of age

Visiting physician Does the presence or absence of a thrill aid in the diagnosis of arteriovenous fistula? Dr Horton A bruit or a thrill is of importance if it is present. Its absence, however, does not exclude the presence of an arteriovenous fistula In this series of forty cases, which I have just studied, bruits were present in only ten, so that if one depended on the presence of a bruit to confirm the diagnosis, one would have missed the diagnosis in thirty of these cases

Visiting physician If there are not any ulcers or gangrene, is there anything to worry about in permitting the patient to go without treatment? Dr Horton Arteriovenous fistula not only produces local and regional manifestations in the involved extremity, but also frequently produces systemic manifestations and this is indicated by increased pulse rate and hypertrophy of the heart This is an important point to remember From the standpoint of the heart, the lesion is similar to, but not identical with, aortic insufficiency In this particular case, the heart was enlarged to grade 1

Visiting physician Does the demonstration of arterial blood in the veins require laboratory equipment? Can it be done by the average physician? Dr Horton The final diagnosis of arteriovenous fistula rests on the demonstration of a high admixture of arterial and venous blood in the veins of the involved extremity In the average case it is only necessary to withdraw blood from one of the dilated regional veins in the affected extremity and to compare its color with blood which has been withdrawn from a vein of the corresponding normal extremity, in order to establish a diagnosis Blood from the regional veins of the affected extremity is invariably bright red, indicating its arterial character, whereas, blood

from veins of the normal extremity is dark red In doubtful cases, gasometric determinations of oxygen content should be made A method that is being used at present as I have said, is arteriography, but it was not necessary to use it for diagnosis in this case It may yet be useful in this case to determine whether or not the fistula is susceptible of surgical treatment

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DISEASES OF THE VEINS

NELSON W BARKER

In order to orient ourselves in the general field of diseases of the veins, I would like to present a tentative clinical classification (Table 1)

Some of these conditions are rather rare whereas others are common For practical purposes, thrombophlebitis and primary and secondary varicose veins are the only ones of importance This discussion is limited to diseases of the veins

TABLE 1

TENTATIVE CLASSIFICATION OF DISEASES OF VEINS

Obstructive	Intrinsic	Inflammation, thrombophlebitis
		Neoplasm, direct invasion
	Extrinsic (pressure)	Gravid uterus
		Neoplasm
		Arterial aneurysm
		Anomaly of contiguous structure
		Trauma to contiguous structure
Nondestructive	Valvular	Primary varicose veins
	Traumatic	Arteriovenous fistula
		Rupture
	Congenital	Arteriovenous fistula
		Phlebectasia
		Hygroma
	Degenerative	Phlebosclerosis

of the extremities because affection of the veins of particular viscera are usually considered with diseases of those viscera Diseases of veins of the lower extremities are the most important and will be considered first

LOWER EXTREMITIES

Varicose veins are commonly seen in medical practice They may be primary in cause or secondary to increased

venous pressure from obstruction of the more proximal venous trunks Any of the obstructive lesions of veins may produce secondary varicose veins, but the most common causes are pregnancy and thrombophlebitis In the former instance the obstruction is transient, but the veins are permanently injured Extensive obstructive lesions of veins are not necessarily fol lowed by varicosities When they do develop, it seems prob able that the walls of the individual's veins, or the valves, are congenitally inferior and do not stand up under the strain of increased pressure from proximal obstruction It is common to find successive members of the same family who have vari cose veins as the result either of obstructive conditions, or spontaneously Occupation is often a definite contributing cause of primary varicose veins They frequently affect nurses, waitresses, and persons who spend a great deal of time on their feet Obesity seems to be a contributing cause in many cases but varicose veins may also develop as the result of senile atrophy of the tissues of the legs The subcutaneous fat is absorbed, and without this external support the vein gradually dilates and the valve becomes incompetent The possibility of infectious or toxic injury of valves, as a cause of primary varices, is doubtful

There are several clinical types of varicose veins Groups of dilated, small cutaneous veins or venules, sometimes called "spider nevi" or "telangiectases," are often seen but are of little clinical significance Localized saccular varices are some-times seen, and if situated just below Poupart's ligament may be mistaken for a femoral hernia Multiple varices, involv-ing many medium-sized, superficial veins of a limb, are likely to be secondary to some obstructive lesions of veins, and are the most difficult to treat The localized tortuous varices in-volving portions of the long or short saphenous veins and their immediate tributaries are the most satisfactory to treat by injection, particularly if Trendelenburg's test is positive Tren-delenburg's test is for competence of valves After elevation of the leg and drainage of the veins, the saphenous vein is compressed above the varices while the patient assumes the

upright posture again After fifteen seconds the pressure is suddenly released A positive test is indicated by rapid filling of the varices from above Filling of the varices before the pressure is removed, indicates reversed flow between the deep and superficial veins and is called a negative test Absence of rapid filling of the veins, both before and after removal of the pressure, is called a "Trendelenburg nil," and is normal, indicating competent valves

Varicose veins may be simple, or they may be complicated by chronic venous decompensation or chronic venous insufficiency of the limb This occurs when the back pressure and congestion, augmented by the upright posture (walking and standing), become so great that the tissue fluids cannot be adequately drained by the lymphatic channels It is manifested first by cyanosis and edema, and later by acute or chronic indurative cellulitis, necrosis and ulceration of the skin, eczema, and pigmentation Thrombosis may occur spontaneously in varicose veins, or as the result of trauma Simple varicose veins do not usually produce symptoms In the complicated types, there may be varying amounts of pain in regions of ulceration, induration or inflammation, and sometimes a muscular ache after walking, which can be relieved by elevation of the limb

The diagnosis of varicose veins is usually apparent It should be borne in mind that occasionally the varices may be secondary to some external obstructive lesion of a proximal vein, such as the iliac vein or the vena cava and careful general examination should be made to exclude such a lesion Rarely, the dilated veins secondary to an arteriovenous fistula are mistaken for simple varices The presence of an arteriovenous fistula may be suspected from the history of the development of the distended veins soon after birth or after a penetrating wound of the extremity and by the presence of thrills and bruits The diagnosis may be settled by the finding of bright red blood with high oxygen content in the veins and by arteriography (Horton)

The treatment of varicose veins may be divided into three

parts (1) simple measures, (2) sclerosing injections, and (3) treatment of complications Uncomplicated, simple, small varices may require no treatment, but they may be forerunners of more serious trouble Less walking and standing, if practicable, should be urged Constricting garters should be avoided Sitting with the legs elevated should be cultivated as a habit Avoidance of trauma to the legs is important The injection treatment has been very successful in many cases, and has revolutionized the treatment of varicose veins by almost completely supplanting surgical procedures Many articles have appeared in the literature on this subject It must be borne in mind that there are certain contraindications to injection treatment These include the presence of occlusive arterial disease of the leg, the recent (within three months) occurrence of spontaneous thrombophlebitis of any veins, the presence of acute infectious disease, the presence of congestive heart failure or other severe systemic disease, and the presence of extensive, chronic venous obstruction of the femoral or iliac vein, such as that which follows extensive thrombophlebitis A number of sclerosing solutions have been used in the treatment, of these, according to F L Smith, sodium morrhuate appears to be the safest and most satisfactory Quinine and urethane is also extensively used

Stasis-edema, complicating varicose veins, may or may not disappear after treatment by injection If it persists, it should be controlled by a supportive bandage or stocking, for it may be a forerunner of more serious lesions, such as ulcer and cellulitis It is necessary that the support be comfortable and that it really control the edema No support has been invented that is perfect. Elastic stockings are neat, but the fit must be perfect, and they wear out in a relatively short time Bandages removed and reapplied frequently can be made comfortable, but require some trouble on the part of the patient, and some women object to their appearance Cloth bandages will not control swelling of any considerable degree Heavy, pure rubber bandages are the strongest and most satisfactory supports in the presence of severe edema, but they are hot,

particularly in the summer time The adhesive type of bandage is satisfactory in certain cases, but a new one must be applied at least every six weeks Few patients will tolerate, or be benefited by, a support extending above the knee.

Ulcers from stasis may be treated by careful cleansing and the rubber sponge pressure method of McPheeters and Merkert, either using an adhesive bandage or a removable bandage, and keeping the patient ambulatory This method is superior to the old Unna's paste cast If it fails it may be necessary to put the patient to bed with the leg elevated and to apply warm, moist packs of boric acid or 0 5 per cent solution of aluminum acetate In the most stubborn cases skin grafts may be used provided the ulcer is clean The injection treatment of varices, just proximal to a stasis ulcer, often aids greatly in healing of the ulcer Acute cellulitis is best treated by rest and hot moist packs Chronic cellulitis is a difficult problem, often requiring periods of rest and elevation alternated with adequate bandaging

Thrombophlebitis is essentially an acute disease which produces varying degrees of acute and chronic venous obstruction and venous insufficiency in the affected limb It is extremely rare to see venous thrombosis without some phlebitis or phlebitis without some thrombosis There are four clinical groups of thrombophlebitis, as follows

1 Local Attributable to direct chemical, mechanical infectious, or suppurative trauma or occurring in diseased veins such as varices

2 Hematogenic Associated with blood dyscrasias and primary alterations in the constituents of the blood

3 Secondary Complication of surgical operations child birth various infectious diseases, malignancy and congestive heart failure

4 Primary Idiopathic, spontaneous types and those associated with thrombo-angiitis obliterans

Little is known about the pathogenesis of thrombophlebitis There are three factors which must be considered in its development There is probably some lesion of the vein par

ticularly of the intima This may be a mechanical or a chemical injury, a bacterial infection of the wall of the vein, or the result of a toxin or virus which circulates in the blood Second, there may be an abnormal tendency of the blood to undergo thrombosis Third, there may be abnormal venous stasis, such as occurs in varices, heart disease, or during prolonged rest in bed It is probable that all three factors are present in many cases of secondary thrombophlebitis

Clinically, thrombophlebitis is important because of the disability during the acute stage, the danger of embolus, and the tendency to subsequent development of chronic venous insufficiency of the limb Suppurative types are dangerous and may be the source of infection of the blood stream or pyemia The symptoms, in the acute stage, depend on the situation and extent of the involvement Thrombophlebitis of small, superficial veins may produce nothing more than some local pain and soreness, lasting for a few weeks Involvement of the long or short saphenous veins, if extensive, may cause some edema, particularly in the region of the lower part of the leg drained by these veins When the femoral or iliac veins are involved, there is usually definite swelling and congestion of the leg, with dilatation of the superficial veins, followed, in a few days, by pitting edema At the onset, there is usually considerable pain, not only at the site of the lesion, but also in more distant, congested regions Fever varies, but the temperature is rarely more than 101° F , and chills are rare except in the suppurative types Elevation of pulse rate may be the first symptom

The diagnosis is not usually difficult if one remembers that thrombophlebitis is an acute disease which obstructs veins Superficial thrombophlebitis must be distinguished from erythema nodosum, nodular syphilid, and nodular tuberculid of the extremities Its occurrence, as a primary disease, always should excite the suspicion that thrombo-angiitis obliterans is present, and the arterial circulation should be carefully checked Femoral and iliac thrombophlebitis must be distinguished from acute lymphangitis and cellulitis of the leg

In the latter condition, the leg is red rather than cyanotic, there is usually a chill at the onset high fever and much malaise, and the swelling is brawny Acute arterial occlusion is distinguished by the finding of a cold pale usually shrunken extremity, and pulsations of the peripheral arteries are absent

Pulmonary embolism occurs in a certain number of cases of thrombophlebitis, usually at the on et of thrombosis, and often before the appearance of local symptoms referable to the veins Sometimes it occurs in the course of extension of a thrombus from an already well-developed lesion of a vein Where there is good clinical evidence of inflammation of veins, the thrombus at that point is not likely to break off, but there is always some chance of sudden propagation of the thrombus into a more proximal vein, or of thrombo is suddenly developing in the other limb Practically, however it is unusual to see an embolus occur after the signs of thrombophlebitis are well developed Short saphenous thrombophlebitis is often overlooked and its importance as a source of propagation of a thrombus into the femoral vein should be emphasized Pains in the calf of the leg, after operation particularly should always be regarded with suspicion

If the thrombophlebitis has involved the femoral or the iliac vein, it is likely to be followed by chronic venous insufficiency of the leg This is dependent somewhat on the extent of the original thrombo is, the relative amounts of organization and absorption of the clot, and the ability to develop and make use of the collateral veins Chronic venous insufficiency is manifested at first by increasing static edema when the patient is on his feet, which tends to disappear each night during recumbency The superficial veins remain di tended or collapse readily when the limb is elevated above the level of the heart Secondary varices may develop and be followed by ulceration and cellulitis There may be pain from congestion in the muscles after physical activity The residual swelling in a leg after thrombophlebitis should be distinguished from chronic lymphedema which usually comes on more gradually and is likely to be more firm and indurated in less responsive

to elevation It should also be distinguished from edema of cardiac or of renal origin.

The treatment of thrombophlebitis involves only a few simple procedures For the superficial types, rest and local application of hot packs usually will shorten the course of the disease and relieve pain In femoral or iliac thrombophlebitis, rest is imperative The leg should be elevated to an angle of 30°, and heat in the form of hot, wet blankets covered with rubber sheeting should be applied to the entire leg, from foot to groin Great care should be taken that the packs are not hot enough to burn, and that the skin is kept well greased These procedures should be continued for a week after the temperature has become normal, and until all pitting edema has gone and all local tenderness has subsided Then the patient should be allowed to sit up in a chair a few days, and then to resume normal activity, but from the start the leg should not be dependent without an adequately heavy elastic bandage or stocking If static edema is prevented during the first transition from bed rest to activity, and during the succeeding few months when collateral venous circulation is increasing and canals are forming in the thrombus, the manifestations of chronic venous insufficiency are usually avoided The support must prevent the edema Light-weight cloth bandages are usually inadequate After three months, the support may be left off for half a day as a test If edema occurs, use of the bandage should be continued for another month, and the test repeated If edema does not occur, the bandage may be left off for a longer period If edema does not appear after several days of activity without the support, it may be discarded permanently In a few of the worst cases, it may be necessary for the patient to wear the support indefinitely

Treatment in cases encountered for the first time, in which there are well-developed manifestations and complications of chronic venous insufficiency following thrombophlebitis, is the same as that mentioned previously under complications of varicose veins

UPPER EXTREMITIES

In the upper extremity, the veins are much less subject to disease than are those of the lower extremity. Varicose veins are almost never seen and chronic venous insufficiency rarely develops. Marked dilatation and tortuosity of the veins of the arm and hand are almost always attributable to arteriovenous fistula rather than to simple varix. Thrombophlebitis may occur in the superficial veins of the arm. When not a sequel of mechanical trauma or chemical injury following diagnostic or therapeutic injection of chemicals, it is most commonly a part of thrombo-angiitis obliterans or recurrent idiopathic thrombophlebitis. In both of these conditions there are usually lesions in the lower extremities also. Thrombophlebitis of the axillary and subclavian veins does occur but is relatively rare. An interesting type is the thrombosis or thrombophlebitis attributable to muscular effort or strain of the arm or shoulder occurring usually in young active robust males. It is generally considered to result from compression injury near the site of the subclavio-axillary valve. It may be followed by some permanent dilatation of the superficial veins of the arm and shoulder and some permanent enlargement of the arm. Also, there may be muscular pains after any sustained work or exercise. Slowly developing prominence and distention of the superficial veins of the arm, shoulder, and upper part of the chest are usually attributable to extrinsic venous pressure at the base of the neck from neoplasms and anomalies. If it is bilateral it is usually attributable to compression of the superior vena cava by a neoplasm, and there is also definite congestion and distention of the veins of the neck and face.

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FOUR CLINICAL TYPES OF JAUNDICE ARISING FROM ATYPICAL BLOOD DYSCRASIA

CHARLES H WATKINS

I would like to present four cases rather briefly Many of the laboratory findings in these cases are similar, but the differential diagnosis and suitable treatment have raised important clinical questions

Case I.—A man aged fifty-eight years came to the clinic for a general examination in October 1934 He appeared to be in good health except for a slight yellowish tinge of the skin The blood pressure in millimeters of mercury was 160 systolic and 94 diastolic The pulse and eyegrounds were normal General physical examination did not reveal anything abnormal The liver and spleen were not enlarged The value for hemoglobin was 10 gm per 100 cc of blood There were 2,400,000 erythrocytes and 5,400 leukocytes in each cubic millimeter of blood Twenty four and eight tenths per cent of the erythrocytes were reticulated The erythrocytes were spherical and there was marked microcytosis This type of blood picture is practically pathognomonic of congenital hemolytic jaundice The fragility of the erythrocytes was increased Examination of the stools did not disclose any parasites ova, or occult blood A lateral roentgenogram of the abdomen did not reveal any enlargement of the spleen In view of the fact that there was no family history of jaundice and because the spleen was not enlarged the condition was diagnosed as idiopathic hemolytic icterus. Several blood transfusions were given but the only improvement which was noted was an increase of about 1,000,000 erythrocytes per cubic millimeter of blood

The patient went home but returned in about a month At this time the condition of his blood was approximately the same as it was when he first came to the clinic. The value for hemoglobin was 9 gm per 100 cc of blood There were 4,000,000 erythrocytes and 5,000 leukocytes per cubic millimeter of blood The morphology of the erythrocytes was the same as it was before The spleen was not palpable In view of the age of the patient we did not feel that splenectomy was indicated The patient appeared to be getting very weak and we felt that he would get along satisfactorily unless the anemia became more severe than it was It was explained to the patient that in case the anemia became more severe it would be advisable if the anemia became worse than it was Dr and Mrs [illegible] recently have demonstrated that splenectomy results in rather prompt and gratifying recovery of the blood picture in cases of [illegible] hemolytic jaundice It is their opinion that this case should be regarded as a case of [illegible]

hemolytic jaundice, in which hemolysis may be present throughout the entire reticulo-endothelial system instead of being confined chiefly to the spleen

Case II.—A woman, aged thirty-one years, came to the clinic in March, 1934. She recently had had an attack of diarrhea, which had been diagnosed as intestinal influenza.

A palpable spleen was the only abnormality that was discovered in the course of general physical examination. There was not any history of jaundice, and the liver was not enlarged. The value for hemoglobin was 13.9 gm. per 100 c.c. of blood. There were 4,400,000 erythrocytes and 7,500 leukocytes per cubic millimeter of blood. Three and a half per cent of the erythrocytes were reticulated. The number of blood platelets and the bleeding time were normal. Examination of blood smears revealed spherical erythrocytes, the presence of microcytosis, and evidence of active regeneration. This is the type of blood picture that is seen in hemolytic jaundice. However, there was definite immaturity of the granular leukocytes, neutrophilic metamyelocytes, myelocytes, and promyelocytes being present. Since there was not sufficient regeneration to account for this finding, we did not believe that definite diagnosis of hemolytic jaundice was justified. Immaturity of this degree does not occur in such cases unless there is marked evidence of hemolysis. The value for serum bilirubin was 1.8 mg. per 100 c.c., by the indirect reaction. Fragility of the erythrocytes was increased.

The patient went home, but returned to the clinic in October, 1934. At this time, the results of the total blood count were within normal limits. Reticulated erythrocytes comprised 3.7 per cent of the erythrocytes. Examination of blood smears disclosed that 5.5 per cent of the leukocytes were metamyelocytes, 0.5 per cent were myelocytes, 0.5 per cent were promyelocytes, and 2 per cent were leukoblasts. It therefore was assumed that the patient had low-grade chronic myelogenous leukemia.

The patient again returned to the clinic for examination in January, 1935. At this time, there was still slight immaturity of the myeloid elements, the splenomegaly was of about the same degree as it was before, and the fragility of the erythrocytes was greater than it was before. I have seen similar cases of early chronic myelogenous leukemia, which had the early hematologic features and some of the clinical features of hemolytic jaundice. A typical leukemic state eventually developed in these cases.

Question. What caused you to suspect that this patient had a disease of the hematopoietic system when you first saw her? Dr. Watkins. The splenomegaly.

Question. What were the symptoms? Dr. Watkins. She came to the clinic on account of diarrhea, which had been diagnosed as intestinal influenza.

Question. What is your opinion about the prognosis? Dr. Watkins. I think that the prognosis is poor, although the patient probably will live about three years longer than will the

average patient who has leukemia The immaturity of the leukocytes is increasing, and leukocytosis probably will de velop ultimately

Question Do patients who are suffering from leukemia have splenomegaly early in the course of the disease? Dr Watkins Some of them do not Examination of the eye grounds frequently enables us to detect such cases when no other clinical signs of leukemia are present

Question What are the ocular findings in leukemia? Dr Watkins Hemorrhages and infiltration into the retina The most characteristic hemorrhages are those which have an associated central or peripheral zone of infiltration Infiltration often is situated along the peripheral vein

Case III.—A woman aged thirty years was seen elsewhere in consultation She had always enjoyed good health except for mild hypochromic anemia which never had caused her any inconvenience The value for hemoglobin never had been less than 60 per cent or more than 70 per cent by Dare's method

Following an operation for deflected nasal septum profuse epistaxis had developed There had not been any evidence of an abnormality of coagulation of the blood before operation A transfusion of 500 cc of blood from a group IV donor had been given Eight hours after the transfusion mild jaundice had developed and the spleen had become enlarged The anemia had become more severe than it had been before the transfusion The epistaxis had continued and another transfusion of 500 cc of blood had been given Inasmuch as the blood of the patient also belonged to group II the blood for this transfusion had been obtained from a group II donor Following this transfusion the anemia had become more severe than it had been before the jaundice had increased and the liver had been found to extend about 4 inches (10 cm) below the right costal margin The value for hemoglobin had been found to be 6.5 gm per 100 cc of blood at this time A blood count which had been made at this time had disclosed that there were 500,000 erythrocytes and 31,000 leukocytes per cubic millimeter of blood The epistaxis had ceased and the enlargement of the spleen had been graded 4 on a scale of 4 A transfusion of 450 cc of blood had been given at this time After the transfusion, the jaundice had increased and the liver and spleen had increased in size A blood count which had been made at this time had revealed that there were 1,000,000 erythrocytes and 45,000 leukocytes per cubic millimeter The value for hemoglobin had been found to be 6 gm per 100 cc The fragility of the erythrocytes had been found to be increased Examination of the films which were taken at this time had revealed the presence of the granular leukocytes normally found in the bone marrow and not in the blood Hemorrhages

majority of the granular leukocytes had been found to be mature The erythrocytes had exhibited microcytosis of the biconcave type A diagnosis of chronic myelogenous leukemia had been made A fourth transfusion of blood had been given The blood had been obtained from a group IV donor

I saw the patient on the evening of the day on which the fourth transfusion of blood had been given The blood count at this time revealed 450,000 erythrocytes and 78,000 leukocytes per cubic millimeter of blood Many myeloblasts were present and there was marked evidence of regeneration. Ninety-four per cent of the erythrocytes were of the reticulated variety and there was a general microcytosis, accounted for by cells of the biconcave type. The spleen was enlarged to grade 4, and the edge of the liver extended to the level of the umbilicus

The diagnosis obviously is acute hemolytic crisis I have seen this condition affect individuals whose blood belongs to group II more often than I have seen it affect the blood of individuals whose blood belongs to one of the other groups, but, so far as I am aware, this is coincidental and is not the result of a specific group reaction

The treatment is chiefly palliative Transfusion should be avoided Fluids, other than blood, should be administered intravenously to maintain the blood volume

The patient made an uneventful recovery in about two months Examination of the blood at the end of this period did not reveal any anemia or microcytosis, and disclosed that fragility of the erythrocytes was normal The spleen and liver could not be palpated at this time The patient is in excellent health at the present time

Question What caused one physician to make a diagnosis of leukemia? Dr Watkins The immaturity of the leukocytes and the leukocytosis She did not have leukemia, if she had had leukemia, there would have been a higher percentage of myeloblasts than there was

Question What was the percentage of polymorphonuclear neutrophils? Dr Watkins It was very high

Case IV —A woman, aged fifty-one years, was referred to the clinic with a tentative diagnosis of hemolytic anemia She always had enjoyed good health until a year before, when she had noted a "tired-out" feeling Since this time, she had become exhausted more easily than before These symptoms had been especially pronounced during the last five months She had consulted her local physician, who had found that the value for hemoglobin was 30 per cent, and that there were 1,000,000 erythrocytes and 8,000 leukocytes per cubic millimeter of blood The skin had had a peculiar yellowish tinge, and a tentative diagnosis of pernicious anemia had been made Adequate doses of liver extract (Lederle) had been administered intramuscularly This treatment had not produced any improvement in the general condition or in the anemia A combination of iron and liver extract (Lederle) then had been administered

lat this had failed to change the general condition The patient then was referred to the clinic by her family physician

Physical examination revealed that the patient was extremely obese. There was a sense of resistance in the left upper quadrant of the abdomen but the spleen could not be palpated definitely The value for hemoglobin was 5.6 gm per 100 c.c of blood There were 1 4 0,000 erythrocytes and 6,200 leukocytes per cubic millimeter of blood Examination of blood smears disclosed that there was a marked increase in the regeneration of erythrocytes which was indicated by the presence of anisocytosis and polychromatophilia The percentage of reticulated erythrocytes was 44 9 Myelocytes were present but there was not any spherical microcytosis The fragility of the erythrocytes was increased definitely The coagulation time and clot retraction were normal. The value for the serum bilirubin was 2 8 gm per 100 c Its the indirect reaction. The condition was diagnosed as hemolytic icterus the acquired type This diagnosis was based on the history of a progressive anemia which had failed to improve as a result of adequate treatment for secondary or for pernicious anemia the increased fragility of the erythrocyte the increased regeneration of the erythrocytes the absence of spherical microcytosis and the absence of a family history of jaundice It was felt that splenectomy would improve the condition but because of the marked obesity and the poor physical condition of the patient and because of the danger of blood transfusion in this type of case it was decided that the operative risk was too great to warrant such a procedure The patient returned to her home She was advised to follow a reducing regimen and to return to the clinic for further observation

COMMENT

These cases represent four clinical types of jaundice The first case evidently is one of hemolytic jaundice without splenomegaly In view of the absence of immaturity of the leukocytes, and the absence of other features of leukemia it was felt that this diagnosis was warranted

The second case, which is representative of chronic myelogenous leukemia in the very early stages, shows some of the features of hemolytic jaundice

In the third case the clinical picture is characteristic of an acute hemolytic crisis, which may be confused with a leukemic process However, the diagnosis usually can be made easily by the history of attacks of jaundice and progressive anemia, which follow the transfusion of blood

In the last case, the patient apparently had an acquired type of hemolytic jaundice It would be interesting to know how this patient would react to splenectomy but on account of the marked obesity and poor physical condition of the pa

tient, the operative risk was considered too great to warrant such a procedure

Question What is your opinion of the therapeutic value of splenectomy in the four cases that you have presented? Dr Watkins In the first case, the anemia was not severe and there was little evidence that the hemolytic process was very active, therefore, it was not felt that splenectomy was indicated The patient appeared to be getting along very satisfactorily, and since the operative risk of splenectomy is relatively high, particularly in cases in which the patient is as old as the patient in this case was, it seemed unwise to take this risk

When splenectomy has been performed in cases similar to Case II, it has been followed by a marked exacerbation of the general condition, by leukocytosis, and by a more or less rapid appearance of the typical features of chronic myelogenous leukemia For this reason, splenectomy was considered to be contraindicated in Case II

In Case III, splenectomy was contraindicated on account of the extreme degree of anemia. If the patient had been seen earlier than she was seen, splenectomy probably would have been advisable

In Case IV, in which the patient had an acquired type of hemolytic jaundice, splenectomy probably would have been performed if the physical condition of the patient had not been so bad that the procedure was considered to be too much of a risk Splenectomy possibly might have stopped the active destruction of erythrocytes, and might have produced gradual remission of the anemia

Question What therapy did you use for the hemolytic crisis in Case III? Dr Watkins Intravenous administration of dextrose in physiologic saline solution, and the intravenous administration of a solution of acacia

Question Do you think that the acacia accomplished anything? Dr Watkins I am not sure, but perhaps it did I have observed that, in acute hemorrhagic conditions, acacia supports the circulation until a suitable donor can be obtained for a blood transfusion

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A CLINIC ON SOME DISEASES OF JOINTS

I Gonorrheal arthritis, results of fever therapy
II Acute postoperative arthritis, its identification
III Acute postoperative gout, its treatment and prevention
IV The inactivating effect of jaundice in chronic infectious (atrophic) arthritis and fibrositis.

PHILIP S HENCH

May I discuss with you this morning the four cases illustrative of widely diverse diseases of joints and their treatment

I. GONORRHEAL ARTHRITIS; RESULTS OF FEVER THERAPY

It is indeed fortunate that joints become involved in only a small percentage of cases of gonorrhea because when gonorrheal arthritis does occur the likelihood of considerable residual injury to the joint has, up to the present time at least, been great Those of you who have cared for patients with acute gonorrheal arthritis will agree that you generally did not expect the patient to be able to use the joint with any comfort for several weeks Even then the patient had, unfortunately too often, a lasting souvenir of his experience, by way of a permanently thickened and sometimes very stiff joint Now with the advent of fever therapy, it would seem that such residues can be almost entirely prevented and that rapid restoration of joint function generally can be provided for the results of fever therapy in acute gonorrheal arthritis have been very good as the following case will illustrate

CASE I.—Dr Alexander McLean This patient a thirty year old lawyer had several attacks of gonorrheal urethritis with resultant [illegible] In January 1933 he had another attack When the discharge had become

diminish as the result of treatment, migratory polyarticular "arthritis" suddenly appeared, involving shoulders, neck, an elbow, knees, a hip, and the right ankle joint Fever was present After two days the pain disappeared from all these joints except the right ankle and foot, where it seemed to settle, the ankle and foot were very painful, red and swollen for two or three weeks Then the inflammation therein began to subside, the joints becoming apparently normal after six weeks Under local treatment the urethral discharge stopped

After further sexual exposure the urethral discharge reappeared two years later, in December, 1934 Gonococci were present in smears Since an examination of his companion was negative, the patient assumed his attack was not from a reinfection but was a recrudescence of old, quiescent infection In January, 1935, one month after reappearance of the discharge, his knees, shoulders, and hips began to ache and feel stiff On February 15, pains in these joints increased but particularly in the right ankle, which became very red and swollen After a few days the pains began to recede in all affected joints but the ankle The condition of this region has become steadily worse

On the patient's admission to the clinic, February 19, 1935, physical examination gave essentially negative results, except for the presence of some fever (101° F), an infected prostate and urethra, and a hot, very painful, tender, and swollen right ankle, of which the tarsal and subastragaloid (subtalus) joints were affected The metatarsals of the right foot were inflamed to a lesser degree A roentgenogram of the right ankle and foot gave no evidence of bony changes Smears of the urethral discharge revealed gonococci The Wassermann reaction was negative The leukocytes numbered 10,600 per cubic millimeter of blood The sedimentation rate was 65 mm at the end of one hour The urine contained albumin grade 1, pus cells grade 2

A diagnosis of acute gonorrheal arthritis and acute recurrent gonorrheal urethritis was made

Management of the case Dr Hench The patient has been given five sessions of fever therapy of about five to seven hours each, at about 106° to 106 8° F The sessions were given on February 22 and 26, March 1 and 5 The last session was given yesterday, March 8 An examination the morning of the first session of fever revealed the following Right tarsal joint red (grade 2), swollen (grade 2), tender (grade 3), stiff (grade 3), and painful (grade 3) on voluntary and forced motion Right subastragaloid joint, red (grade 1), swollen (grade 2), tender (grade 2), stiff (grade 3), and painful (grade 3) on voluntary and forced motion There was also involvement of the metatarsals, grade 1 to 2 The man avoided all walking, as it was very painful, but in motion pictures, taken the day before the first session of fever, the man

can be seen limping painfully with the help of a borrowed cane (Fig 69, *a*)

The patient was in the fever cabinet only two hours when he noticed some relief of pain At the end of the first session

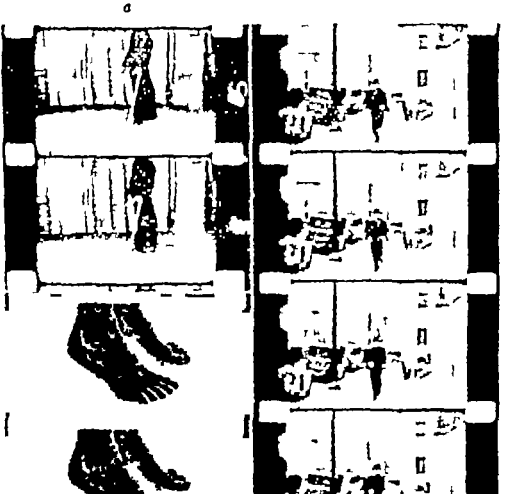
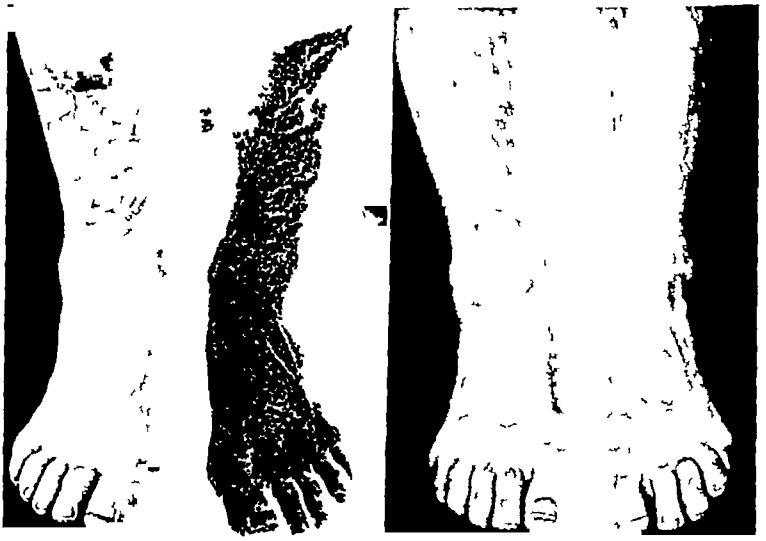


Fig 69—Case 1 Motion picture strip showing results of fever therapy in a case of gonorrheal arthritis *a* Patient walking painfully with a cane February 2 1911 before the first session of fever *b* forty-eight hours after first session of fever the patient was able to walk on the toes also he could walk freely *c* fifteen days after the first session—patient running on the street

he was able to walk to his room with only a little pain Motion pictures taken forty-eight hours later show him walking readily with practically no pain or tenderness even on strong passive motion You see him rising high on the toes of his right foot bearing his full weight thereon with ease (Fig

69, *b*) The second session was given, February 26, four days after the first On the next day urethral smears were negative for gonococci although a slight, watery discharge persisted The joints were entirely free of pain Between the third and fourth sessions of fever the man walked a mile and a half to the station in order to spend the week-end at home, after which walk he noted slight tenderness over the internal mal-



a *b*

Fig 70—Case I Results of fever therapy in a case of gonorrheal arthritis *a*, The right ankle is swollen (grade 2) before fever therapy, the left foot was not affected, *b* (photograph taken fifteen days after *a*), after a course of fever therapy the condition and appearance of the affected ankle is essentially normal, only slight, painless thickening remains

leolus for one day He is now ready for dismissal (March 9), having had his fifth session of fever yesterday Two more urethral smears have shown no gonococci and none have been found on culture of the expressed secretion The joints are entirely pain-free even on forced motion and heavy pressure While there still remains a little thickening, he has full range of motion in the joints of the foot and ankle He can jump up and down on the previously affected foot without any pain

whatever He smiles, instead of wincing when I use strong pressure on his ankle and move it with considerable force Compare the essentially normal appearance of the ankle today with its swollen appearance of two weeks ago as shown in the photograph (Fig 70)

This morning we took a motion picture of this patient sprinting rapidly up the street (Fig 69, *c*) He is able to do this, fifteen days after our first motion pictures were taken, which then revealed him walking but a few steps slowly, with a cane, limping badly, and wincing sharply to slight pressure over his ankle *

A physician You mention making cultures for gonococci Aren't cultures very difficult to grow and of less diagnostic help than the examination of smears?

Dr Hench Formerly yes New culture methods are a great improvement over old ones and give very good results McLeod and his associates devised a method recently approved by Leahy and Carpenter and simplified by Dr Luther Thompson of this clinic, which includes incubating the cultures in an atmosphere of carbon dioxide With this it is possible to isolate and grow gonococci from discharges even when direct smears are apparently negative Now we are relying more on culture determinations of cure than we are on smears

A physician In this case why did you persist in giving two or three additional sessions of fever after the joints were apparently normal and the urethral smears had become negative?

Dr Hench There are differences of opinion as to how many sessions are needed It seems to be generally agreed that three to five sessions are required the last one or two being given to "mop up" any hidden infection that may have escaped detection by clinical or bacteriologic examination Perhaps he really didn't need the last two sessions and might have gotten along just as well without them Further experience will show us the minimal and maximal requirements

*In a letter dated April 15 the patient was reported "just as well as ever Can walk as well as ever"

In occasional cases in which the infection is from a particularly heat-resistant strain of gonococcus, the joints may or may not clear up after two or three sessions, but several more sessions, up to a total of ten or more, may, in the experience of Desjardins, Stuhler, and Popp, be required to sterilize the more resistant infections of the genito-urinary tract In general, urethral smears become negative after from one to three sessions of fever

Comment on diagnosis Dr Hench You will recall that this patient has had gonorrheal rheumatism twice On both occasions it was first manifested by an acute, febrile, somewhat migratory polyarticular involvement which lasted for several days Then the disease disappeared from all but one region (rather than one joint, for the tarsal and adjacent subastragaloid joint and to a slight extent the metatarsals remained affected) It seems to be rather a widespread impression that gonorrhea, like tuberculosis, almost always produces monarthritis, and that when polyarthritis is present, its nature is probably not gonorrheal in origin, and gonorrhea need not be considered in differential diagnosis

Gonorrhea may produce monarthritis, which may arise unaccompanied by a preliminary polyarticular affection However it often arises, as in this case, out of the midst of fading polyarthritis or "polyarthralgia," suddenly emerging like a buxom soloist out of the background of a retreating chorus If the patient had not volunteered full information on his case, and if we had seen him in the early febrile phase characterized by migratory polyarticular pain we might well have made a mistaken diagnosis of acute rheumatic fever I have seen the mistake made and have made it myself, only to be rudely jolted out of my complacency when the salicylates which seemed to be driving the pains of "rheumatic fever" out of most of the joints failed to cure one stubborn joint which persisted in remaining acutely sore When such an eventuality arises, if one appreciates its possible significance, one still has the opportunity of retrieving a correct diagnosis by appropriate, if embarrassingly late, inquiries and investiga-

tion This mistake is particularly likely to occur when, with an innocent air, an attractive patient deliberately conceals pertinent data I suspect that a good many cases in which residual chronic arthritis resulted from acute rheumatic fever' (which the majority of physicians believe rarely if ever produces chronic arthritis) could have been dismissed with a better diagnosis

In the chronic arthritides one has so much of the clinical pattern behind one to consider in connection with obvious pathologic change, that classification within the limits of our knowledge is usually not difficult and generally can be made readily on the first examination in a given case In cases of acute arthritis the clinical pattern is just developing Only a brief fragment of it may be as yet exposed to view In such a situation it is of course well not to make a diagnosis on the first examination but merely to form an impression,' some idea on which to start treatment, and to keep one's mind open and ready to change that impression in accordance with the development of the case

Joints become involved in about 3 to 5 per cent of cases of gonorrhea Thus of 13,000 cases of gonorrhea recently reported by Lees, in 388 (about 3 per cent) articular complications developed The symptoms of gonorrheal rheumatism are variable, depending on the virulence of the infecting agent and the resistance of tissues According to Lees acute involvement of joints with gonorrhea is classified as follows (1) arthralgia of one or more joints, (2) acute synovitis (3) acute arthritis in which cartilage synovial capsule, and periarticular tissues are involved and a serofibrinous exudate is present (such acute arthritis of one or more joints may follow a few days of flitting arthralgia) (4) acute purulent arthritis a rare complication which may result from gonococci alone not necessarily from a mixed infection Subacute and chronic cases may be of two types (1) synovitis (2) arthritis with involvement of cartilage synovial and periarticular tissues

Arthralgia may represent merely a toxic effect When

joint exudates arise, actual articular invasion with gonococci probably has occurred In 80 per cent of Lees' cases of gonorrheal arthritis, articular manifestations occurred within the first four to five weeks of the primary infection It was seen as early as the fifth day of acute urethritis, but in cases of chronic genito-urinary infection, the onset of arthritis may be much later

Polyarticular involvement was present in 58 per cent of Cooperman's seventy cases, in 67 per cent of Wehrbein's 610 cases, in 80 per cent of Keefer and Myers' sixty-nine cases and in 85 per cent of Lees' 388 cases In the latter cases the order of frequency of involvement was knee in 64 per cent, ankle in 37 per cent, metatarsophalangeal joints in 35 per cent, shoulder in 23 per cent, wrist in 14 per cent, metacarpophalangeal joints in 14 per cent, elbow in 12 per cent, hip in 4 per cent, intervertebral joints in 3 per cent, temporo mandibular joint in 2 per cent These percentages are in general agreement with those of others (Pugh, Wehrbein, Keefer and Myers)

A physician You have not mentioned sternoclavicular joint involvement Isn't this a common site for gonorrheal arthritis or at least when this joint is involved, isn't it generally a gonococcal involvement?

Dr Hench Apparently not, at least statistics would suggest that this joint is involved in only 3 per cent or less of cases of gonorrheal arthritis

Experiences with fever therapy in gonorrheal arthritis Dr Hench Doctors Slocumb, Popp, and I[0] recently summarized our results with this type of treatment in sixteen cases, nine of acute and seven of chronic, gonorrheal arthritis The average duration of arthritis was thirteen days in acute cases, twelve months in chronic cases In five cases the arthritis was very severe (grade 4), in four it was severe (grade 3) It was moderately active (grade 2) in five, and mild (grade 1) in two Many of the joints were exquisitely tender, markedly swollen, and indurated, and were held almost entirely immobile because of pain In four cases poly-

arthritis was present, in the others only one or two joints were involved

In general, these patients were subjected to three or four sessions of fever, each lasting about five hours after a temperature of 106° to 106.8° F. had been reached. The Kettering hypertherm was used. This is a large air conditioned cabinet through which heated, humidified air is forced. At the conclusion of the course of fever therapy 69 per cent of the sixteen patients were entirely or practically symptom free, an additional 17 per cent were markedly relieved. Thus of the sixteen patients, fourteen received an excellent result. Only two were not so benefited, both had chronic gonorrheal arthritis. Of the nine patients who had acute gonorrheal arthritis eight (88 per cent) were promptly and completely relieved or practically so, an occasional one noting but the lightest tenderness on deep pressure or a very mild ache on full activity. The remaining 12 per cent were markedly relieved. Thus in 100 per cent of these cases fever therapy was very effective. Several months later the relief had been maintained.

These results are in agreement with those previously reported by others. Since the first reports in 1927 by Carpenter and Warren, and by Bishop Horton and Warren a total of nine reports have appeared from six groups of workers. Of the cases mentioned therein data on results in a total of twenty four cases are specifically given. Of these twenty four cases apparently in twenty two (92 per cent) the patients were promptly and completely relieved or cured. Failure resulted in only two cases (8 per cent) and was attributable to inadequate doses of fever.

Physician. How do the results of fever therapy in cases of chronic infectious (atrophic) arthritis compare with those in gonorrheal arthritis?

have been by other measures However, a trial of fever therapy in selected cases is justified, particularly if the arthritis is of less than one year's duration

II ACUTE POSTOPERATIVE ARTHRITIS, ITS IDENTIFICATION

Shortly after the arthritic service was established, about thirteen years ago, I began to be called to the surgical floors to see occasional patients who, a very few days after operations of various sorts, had acute, painful arthritis as a postoperative complication The arthritis occasionally was polyarticular, more frequently, monarticular Thinking, with a defensive attitude, in terms of infection or of postoperative sepsis, I at first favored a diagnosis of acute postoperative infectious arthritis, suspecting that at the time of operation on some infected region these patients had gotten some absorption, a temporary bacteremia incident to the necessary manipulations of surgery, and then a metastatic joint infection We were considerably worried lest residual damage occur in the joints, wondering exactly what type of infection we were dealing with, and how to prevent and treat it, but by the time our anxiety reached its height the arthritis practically always promptly faded away We were relieved to find that the affected joint or joints generally cleared up completely after a few days

In retrospect, it seems that we were rather obtuse in not recognizing the nature of the affection sooner, but we at least soon reached the stage at which we could view such a postoperative complication without trepidation, and assure the patient and the surgeon that whatever it was, it would in all likelihood soon go away completely After a few of these experiences we were able to identify acute postoperative arthritis, and in the past ten years we have studied about fifty such cases With few exceptions they all clearly belong to one type of disease of which the following case is an illustration

Case II.—Dr McEwan A male Syrian, aged fifty-nine years, was first admitted to the clinic, November 5, 1934, for treatment of an epithelioma of the cheek which had been present for many years but which recently had

begun to enlarge According to his history, given at this time he had no other disability His physical examination was essentially negative except that there was a tumor and firm palpable glands in the neck

November 7, under infiltration anesthesia a squamous-cell epithelioma was removed by surgical diathermy Radium was applied About forty hours after operation the man was wakened in the night (November 8 to 9) by aching in the left great toe The pain got worse the next day so that the man couldn't walk, and at night he couldn't sleep The pain in his toe was much worse than the pain from the operation on his cheek There was no fever

The left great toe was tender (grade 3) especially at the mesial aspect of the metatarsophalangeal joint. It was only slightly swollen The right great toe also was swollen (grade 1) tender (grade) and red (grade 1) The left olecranon bursa was thickened but not tender and one or two very small nodules that felt like "rice bodies" were palpated therein.

Roentgenograms showed hypertrophic changes at the right metatarsophalangeal joint of the great toe, similar changes in the left but to a lesser degree The blood uric acid was 4.6 mg per 100 c c Unless the very small bodies in the olecranon bursa were tophi none were found The patient is a heavy drinker and eater He eats meat at least twice a day sometimes a pound at a meal" and partakes of liver once a week He takes three to eight drinks of whisky daily often drinking straight alcohol in addition There is no known history of gout in his family

A diagnosis of presumptive (nontophaceous) gout and acute progressive early arthritis was made

Comment Dr Hench The patient would not permit biopsy of the olecranon bodies and resented the suggestion that he might have acute gout Even though the value for blood uric acid was not particularly elevated (4 6 mg) there could be no doubt of the nature of the trouble the diagnosis of acute gout was based on the various unmistakable characteristics of the attack the sudden onset a few hours after operation, the situation, the shiny, dusky red appearance of the acute arthritis, the characteristic site of maximal tenderness at the mesial, rather than at the dorsal or inferior aspect of the great toe joint, the severity and nocturnal exacerbations of pain, the appearance of the inflammation, first in one great toe and a little later in the great toe of the other foot

Although his history mentioned no such previous experience the presence of a thickened but painless olecranon bursa leads us believe that he must have had an earlier attack of gout which it was the stigma At first he stoutly denied this

until his wife "jogged" his memory, complaining that he lived such a fast life he couldn't keep track of events He then admitted the following In October, 1932, without any known injury, the left olecranon bursa suddenly had begun to swell and become red It was not painful but had enlarged to the size of a lemon In about two weeks the swelling had subsided The patient had been on his feet all day in a store, and in late afternoons would put on heavy tight boots and go hunting in nearby woods As the olecranon bursitis had faded, suddenly pain and swelling had developed in the right great toe He had continued to work at the store, lying on a couch whenever possible because of the severe pain He had persisted in hunting even when he had been obliged to wear slippers and to shoot from the running board of his car A physician had advised application of heat and strapping No diagnosis had been given The attack in the toe had lasted eight weeks and then had subsided completely as far as symptoms were concerned, but there had been residual thickening of the metatarsophalangeal joint

Two years later, in October, 1934, a month before admission here, after a day's hunting in tight boots, he had awakened in the night with severe burning pain, swelling, and redness of the midphalangeal joint of the second left toe He had been in bed for three days, the pain being much worse at night There had been no fever No physician had been consulted The condition soon had subsided entirely

These additional data revealed the characteristic pattern of gouty arthritis, recurrent acute attacks with complete remissions, which made us more certain of the diagnosis After three days' treatment with wine of colchicum, cinchophen (with sugar, alkalies, and water), and a purine-free diet, the pain in the left toe subsided entirely, although slight (grade 1) tenderness persisted in the right great toe a few days thereafter December 10, the value for blood uric acid was 4 3 mg per 100 c c With such a therapeutic response, the clinical diagnosis of gout seemed entirely proved The man was told that when he returned for surgical removal of the cervical

glands he was to be especially careful of his diet and to take cinchophen for a few days before operation He was dismissed to follow a low purine diet, and with instructions to take cinchophen 7½ grains (about 0 5 gm) three times a day, three consecutive days each week

The man stopped taking cinchophen in about three weeks He still refused to accept the diagnosis of gout and began to eat more freely and to drink two to three glasses of beer daily to see if the trouble really would come back On the patient's return in January, for removal of the cervical glands, the surgeon had forgotten the patient's previous experience and the patient now admits that he deliberately refrained from reminding him of the, to him, unwelcome advice regarding measures necessary for the prevention of a second postoperative attack

January 16, 1935, under local infiltration anesthesia, block dissection of the glands was performed Metastasis was present On January 19, the third postoperative day pain returned in the left great toe joint and became very severe the next day The toe was tender (grade 3) red (grade 2), very shiny and dusky in appearance and swollen (grade 2) The value for blood uric acid was 4 5 mg per 100 c c on January 21

The patient by now had become in his own words, "very humble" and requested to "put in a hurry up call for those gout doctors" Treatment was instituted at once and in two days the appearance of the toe was again normal although slight tenderness remained

February 2 to 4, 1935, he had roentgenologic treatment over the lymphatics of the neck without experiencing a flareup of his gout

Discussion on diagnosis Dr Hench This is a typical example of so-called acute postoperative arthritis A few hours or days (roughly 20 to 120 hours) after operation the patient gets his attack like a bolt of lightning, out of a clear sky I say 'out of a clear sky' because the patient's postoperative condition up to that time may have been excellent

with little or no postoperative fever or other reaction to give warning of the brewing storm One of the reasons for delay in making an accurate diagnosis is that the patient may never have had an attack before, it took the stress of an operative experience to activate his quiescent disease It is not easy to be certain of the diagnosis in the first attack of gout, particularly if it is in some joint other than a great toe As in this instance, the patient may have had previous gout but he is now concerned with something quite foreign to his past disability and may omit mention of the latter in his history, considering it to be extraneous matter With his perspective altered by the surgical experience through which he has just passed and the "complication" of it, he may not be sympathetic to one's efforts to trace a connection between his present and past attacks of years ago and may occasionally insist frankly that they are different And they may be in some regards At other times he readily recognizes the similarity, and without question accepts the diagnosis of "another attack"

Without the help of a healthy suspicion born of other circumstances, the evidence presented by the appearance of the joints themselves may be hardly adequate to allow the physician to diagnose the condition more than hesitantly But if one remembers that gout is still prevalent, and that surgical operations are one of its most potent determinatives a given case of "acute postoperative arthritis" may be viewed in a different light Then appropriate inquiries and examinations will be made to fortify one's preliminary impression of its gouty nature Without the proper suspicion, however, no estimation of blood uric acid will be ordered, no search for the characteristic history or careful examination for tophi will be made Often the discovery of tophi promptly clinches the matter When they are absent, of particular significance is the elaboration of the patient's past history and the discovery of previous isolated episodes of arthritis which, strung together, form the chain that leads to the correct appraisal of the condition If these, too, are absent, the therapeutic test

must be relied on to clarify matters Too much reliance must not be placed on the diagnostic value of hyperuricemia During two attacks and the interval between them, this patient's blood uric acid was not particularly elevated

Although this patient at first denied any previous attacks our discovery of inactive olecranon bursitis with thickening made us reasonably sure that he had had attacks Olecranon bursitis is at least five times more common with gout than with chronic infectious arthritis Thus on the law of averages olecranon bursitis not adequately explained by trauma, should be the starting point for an investigation for gout Even trauma must not be permitted completely to divert suspicion, for posttraumatic gouty bursitis is not uncommon Success in the management of gout is not infrequently prevented by the patient's refusal to accept the diagnosis and carry out treatment In these days of taxation they resent the implication that they are rich enough to have the disease With the glamor of prohibition removed they dislike to be cloaked with an alcoholic aura This patient probably resented the prescriptions which he knew the diagnosis of gout was to entail in his case And so after his first postoperative experience, he embarked on his own idea of a provocative test, his fear of a day of reckoning being cancelled by his skepticism and the happy anticipation of continuing forbidden pleasures

It is interesting to note that he didn't more promptly come a-cropper that his imbibing of alcohol failed to provoke an attack, and that once more a surgical operation served the purpose in this case the useful purpose of making him malleable In him a chronic drinker alcohol seems temporarily at least to have lost its precipitating punch Dimmill and I have discussed elsewhere the relative potency of the incitors of gout This is another illustration of difference in the ability of a number of varied agents to provoke their The fear that the catabolic process incident to treatment might have precipitated still another attack In this case it did not We have noted however that most often an attack

a patient apparently may be resistant to gout for a while This may or may not explain the harmlessness of his own amateur provocative test and of roentgen therapy

"It was while I was on a hunting (or fishing) trip" This is a familiar phrase in the story of persons with gout, as it is in this man's story It is not unusual to hear that from such an expedition one of our patients has had to be carried home —game, gun, and gout There are several provocative factors incident to such pleasures (1) tight, heavy boots and (2) unaccustomed walking in rough territory, both providing the precipitating factor of trauma, (3) exposure to damp and wet with resultant vasomotor irritability and (4) dietary indiscretions incident to an increased appetite from exercise and to the evenings by the fireside when venison, meats, and liquor form the bulk of the menu

III. ACUTE POSTOPERATIVE GOUT, ITS PREVENTION AND TREATMENT

Dr Hench Of the many differences between gouty arthritis and chronic infectious arthritis, I shall mention three in particular One is the striking difference in sex incidence About 65 per cent of patients who have chronic infectious arthritis are females Gouty arthritis in females is very rare indeed, only about 2 per cent of patients are of this sex[5] Then there is the noticeable difference in the physical appearance of these two groups of patients This is particularly obvious to one who is in daily attendance on large groups of arthritic patients Patients with chronic infectious arthritis are generally thin, somewhat anemic and looked washed-out and sickly We see them one after another in the relative proportions of one unhealthy looking male to two or three unhealthy looking females Then comes a consultation concerning a patient, almost always a male, whose healthy, energetic appearance is in striking contrast to those previously seen Often, before a word has been spoken, one finds oneself instinctively entertaining a snap-diagnosis as the thought suddenly occurs, "Look out for gout here"

Thirdly, there is the striking difference between the two groups in the reaction of their joints after any extra articular surgical operation, whether it be part of the treatment for the arthritis or otherwise Considerable has been said of the dangers of postoperative flareups in cases of chronic infectious arthritis, exacerbations occurring after surgical removal of some focus Flareups occasionally do occur but experience leads me to believe the danger is much over rated In fact, I have come to look on a temporary beneficial effect to the joints as the expected result of almost any surgical procedure, whether it is done specifically for the arthritis or is entirely unrelated and coincidental So generally is this temporary improvement noted that in evaluating such procedures as sympathectomy, cholecystectomy, or other surgical procedures for arthritis, we are inclined to discount as nonspecific considerable of the immediate relief noted, particularly in the first few days Possible factors in production of this relief are the postoperative rest in bed, the convalescent dietary, but especially the vasodilating effect of general or spinal anesthesia A few weeks ago an arthritic patient on our service had a small, benign tumor of the breast excised under ether anesthesia After operation, her joints as she said felt wonderful' for a week and she sought the explanation On being told that it was possibly a temporary beneficence of anesthe in she said, 'Well, why don't you give me a few whiffs of ether every couple weeks, I'd be glad to try it if it would help me that much"

Not so in gout, in striking contrast here generally seen a malevolent, not a beneficent effect from operation Hence our axiom Suspect gout in cases of acute postoperative arthritis Whenever surgery is contemplated in a patient known by us to have gout we insist on a preoperative and an early postoperative regimen as a prophylactic against a postoperative attack In the past several months this regimen has been prescribed in a number of instances and in almost every instance the flareup have been avoided

The following report on a patient who is with us this

morning illustrates again the proclivity of quiescent gout to flareup after operation It includes details of the prophylactic regimen, but in this instance a postoperative exacerbation unfortunately was not avoided

Case III —Dr McEwan This patient is a grocer, aged forty-four years, whose chief complaint on arrival at the clinic, February 14, 1935, was of inflammatory rheumatism His family history is irrelevant

In the spring of 1928, without preceding infection or trauma, severe pain suddenly had developed over night, and redness and swelling had appeared at the metatarsophalangeal (bunion) joint of the great toe The pain had been worse at night and had confined the man to bed for six days He had not had fever His physician had diagnosed the condition as acute inflammatory rheumatism In a few days the condition had entirely disappeared, and the man had been well until six months later Then he had experienced a second attack in the same joint, the attack keeping him in bed ten days, and subsiding completely in a few days thereafter, leaving full joint function

Two years later, in 1930, his third attack had involved the left knee, had been associated with fever, and had been diagnosed hydrops of the knee. Since then the patient has had recurrent attacks at intervals of about six months, generally in the spring and fall At the end of a hard day on his feet he may notice mild tingling of one or the other "bunion joint," and may awake in the morning with a frank attack of acute arthritis therein He is entirely free of symptoms between attacks

He estimates that he has had a total of fourteen attacks in the past seven years, chiefly involving one or the other of the great toes, but also involving each knee separately two or three times He has seen twelve physicians, receiving the diagnoses of rheumatic fever, arthralgic joint, and inflammatory rheumatism One physician, after a preliminary diagnosis of acute infectious arthritis, briefly entertained suspicions that the condition might be gout, and prescribed a low meat diet, but soon reverted to removal of foci of infection and the use of vaccines and salicylates No interval diet or medication has ever been prescribed Three years ago the patient first noted a small swelling on his right ear, the size of a pea

The patient drinks ten to twelve bottles of beer daily About five weeks ago, January 8 1935, after an excess intake of beer one day, he noted redness, tenderness, pain, and swelling of the left foot and ankle By now the inflammation has largely subsided but he comes to see if he cannot avert these repeated episodes

Examination reveals nothing of note aside from the condition of the joints and the nodules on the ears The man has, in general, full motion of all joints, there is no muscular atrophy or articular deformities aside from that of the left metatarsophalangeal joint, which is thickened (grade 2), slightly red (grade 1) but no longer tender The right great toe joint appears normal There is residual thickening of the distal phalangeal joint of the third toe on the right, the site of previous involvement two or three times,

but this toe is not now actively affected Roentgenograms reveal no visible changes in the knees feet or ankles There is a small tophus on the margin of each ear These tophi were opened and revealed the characteristic crystals of sodium urate

The flocculation test gives negative results and results of blood count and urinalysis are normal The sedimentation rate is 3 mm at the end of an hour On admission the value for blood uric acid was 6 mg per 100 c.c

A diagnosis of (1) tophaceous gout and (2) acute (subsiding) recurrent gouty arthritis has been made

Comments on the diagnosis Dr Hench It is the exception for patients with gout whom we see here to have received this diagnosis early in the course of their disease An average of ten to fifteen years generally elapses between onset of the condition and its correct diagnosis* This patient presents all the ear marks (literally as well as figuratively) of gout attacks in the classical situation the big toes, development of the classical and diagnostic pattern of gout, the characteristic rhythm of a series of attacks and complete remissions the attacks often coming in spring and fall, establishment of hyperuricemia, and finally the appearance of tophi In spite of this, the man comes with a diagnosis of inflammatory rheumatism, and while in the past seven years he has been collecting his series of fourteen attacks he has collected almost as many different diagnoses Only one physician suspected gout but he apparently did not have the courage of his convictions and altered the diagnosis Note that, as so often happens, the roentgenograms in this case are of no diagnostic help, even with tophi present

Although the attack was about over when the patient arrived here, the affected toe was still slightly red and swollen and the concentration of blood uric acid was distinctly elevated (6 7 mg per 100 c.c) The man was, therefore, placed on a purine free diet with cinchophen sugar water and soda The foot became normal, and the blood uric acid fell in five days to 3 5 mg (February 19)

At this point the patient decided to have a plastic operation for removal of an old facial scar Because of our previous experiences we warned him that he might experience a

postoperative exacerbation of gouty arthritis but that the attack could probably be prevented if he would carefully carry out, for about five days prior to operation and for at least five days after operation, the following prophylactic regimen a purine-free diet, cinchophen 7½ grains (0 5 gm) three or four times a day (depending on the value for blood uric acid and the clinical activity of the disease), ten to twelve glasses of fluid and a generous intake of carbohydrates daily He elected to have the operation at once although he had taken cinchophen only one day

February 20, the day before the operation, the value for blood uric acid was 3 8 mg per 100 c c He took 7½ grains of cinchophen three times on the day of operation and on the next day (February 21 and 22) but then its administration was discontinued for some reason or other On the evening of February 25, the fourth day after operation, his left great toe began to ache The next day it got increasingly painful, the pain becoming severe by night time Colchicine and cinchophen were given at once The toe was still red the following day (February 27) but the swelling was reduced and the patient could limp to the toilet Two days later the attack had practically subsided and on March 1, 1935, the value for blood uric acid had returned to 2 9 mg per 100 c c

Because acute postoperative gout generally appears within the first five days after operation, we have advised continuation of the strict prophylactic regimen until at least the sixth postoperative day We feel that if this patient had taken more cinchophen before operation and had continued to take cinchophen five days thereafter, he would have escaped the flareup This is one of the very few patients who have not so escaped A summary of the regimen in this case is given in Table 1

A physician You seem quite unafraid to prescribe cinchophen to these patients even at a time when surgery places an additional burden on the liver What is the likelihood of damage from its routine, if intermittent, use in such cases?

Dr Hench It has been estimated that the chances of fatal toxic effects from cinchophen are about 1 500,000 or 1 600,-

000.[10] While the routine use of cinchophen, even when prescribed intermittently, provides some risk to the patient who has gout, we feel that it is a minor and justifiable risk, one which must be taken. Patients who have had but one, or

TABLE 1

DATA ON CASE III

Date	Treatment	Uric acid mg. per 100 c.c. of blood	Urine (24-hour specimen)		Condition of extremities, physical findings, etc.
			Uric acid	Creatinine	
1/15/35		6.7			Typical gouty attack
1/16/35 to 1/17/35	Purine free diet. Cinchophen 7½ grains (0.5 gm.) three times a day				Joint tenderness decreasing
1/19/35	Mercatin injection. Diet continued	3.3			Joint very tender
1/20/35	Metaphen injection. Diet continued				Joint very tender
1/21/35	Plaster cast (thumb to wrist). Local aspirin. Purine free diet. Cinchophen (three times daily)	3.8			Joint greatly improved
1/22/35	Diet discontinued		0.3 gm.	0.3 gm.	Joint tender
1/23/35	Diet continued but no cinchophen taken	3.5	1	1.2	Joint tender
1/24/35	Diet continued. No cinchophen		1	0.9	Joint very tender
1/25/35	Diet continued. No cinchophen		1.4	1.3	Joint somewhat less tender and swollen. Plaster cast removed and joint manipulated
1/26/35	Diet continued. No cinchophen	3.1			Joint tender. Plaster cast applied
1/27/35	Diet discontinued. No cinchophen				Joint tender
1/28/35	Diet continued. No cinchophen				Joint tender
1/29/35	Diet continued. Cinchophen 7½ grains (0.5 gm.) three times a day	4			Joint tender

Perhaps two or three isolated widely separated attacks of gout may get along well on a purine low diet without cinchophen as part of their treatment. However for those whose attacks [illegible] well under vegetarian [illegible]

are generally inadequate to prevent all future attacks and as additional treatment we have found no adequate pharmacologic substitute for derivatives of cinchophen

Of considerably more importance to the life expectancy of the patient than the effect of his disease on his joints is its ultimate effect on the cardiovascular renal system He will not die of gouty arthritis, but some do die of the effects of quietly developing gouty nephritis or of results secondary to the presence of urate stones, or perhaps of coronary disease His mathematical chance of one of these complications developing, although moderate, presents a more real danger than the remote chance of a significant toxic effect developing from cinchophen If he uses cinchophen intermittently, with the precautions noted, he generally gets along so much better and escapes many, often all attacks thereafter, presumably lessening the effect of the disease on kidneys and heart

We are told by some that the so-called precautions, intermittent use of cinchophen and free use of sugar and water on the days it is taken, do not guarantee prevention of toxicity However, we have continued to advise them and have fortunately not seen significant toxic effects on any of a large number of patients with gout treated therewith The coincident oral administration of sodium bicarbonate, enough to alkalinize the urine, is prescribed to prevent the precipitation, in the renal calices or pelves, of excess urates liberated into an acid urine

A physician What is the actual cause of postoperative attacks?

Dr Hench This has not been determined In the inventory of factors to be considered, one could list the possible effect of the anesthetic, the nervous shock of operation, postoperative infection, excess tissue catabolism incident to operation, the postoperative dietary, possibly ketosis, or interference with adequate renal and gastro-intestinal elimination from the narcotics or other agents given after operation Many of these are obviously not the cause and can be ruled out at once Those who have experienced postoperative gout have received

a wide range of local and general anesthetics Few if any, have given evidence of significant shock or infection, indeed in many instances, operations were done on tissues that were not infected The surgical procedures which have precipitated our cases of gout have been of a wide variety including alveolectomy, and prostatectomy, tonsillectomy hemorrhoidectomy, and laparotomy

IV THE INACTIVATION OF CHRONIC INFECTIOUS ARTHRITIS AND FIBROSITIS BY JAUNDICE

Those of us who minister to patients with stubborn, chronic infectious arthritis must often be content with small favors Too infrequently do we experience the thrill of our patients having sudden and relatively complete relief follow on our efforts We are not surprised when mild arthritis of short duration fairly readily responds to treatment and we are fortunately able to provide the means for a definite if gradual improvement in the majority of cases of even well advanced arthritis But we can exhibit no therapeutic tour de force after which this disease becomes promptly and routinely inactivated

Nature, however, occasionally sets the stage for such a quiet drama and may suddenly provide a recession in the activity of the disease that equals, or approximates an overnight cure Whenever such an event transpires it justifies our most thoughtful consideration The following is a case in point

painful, and so weak that she could not turn a doorknob, wring out a wash cloth, or even lift a glass of water with one hand She used two hands for these purposes Pain was present daily and was increased at the approach of a storm

In the summer of 1933 the condition of the joints slowly improved, and relief was practically complete during August After only one month of relief, in September, the wrists again became sore (grade 2), swollen (grade 2), and tender The wrists were still not particularly stiff, but one or two days each week one or the other wrist was so weak as to make the hand "helpless" The ankles also became stiff, particularly in the morning, although they were not red or swollen The woman felt utterly lacking in "pep" on arising, but as the day wore on she felt better, only to feel completely fatigued again by 7 p.m

The condition persisted without improvement during the next summer In August, 1934, the right knee swelled to twice its normal size No redness was present, but the patient had to use a cane for a few days to get around at all, and even walking about the house was difficult Some flexion deformity of the knee was present, inviting the support of a folded blanket for comfort while lying in bed After eight weeks of treatment by rest in bed, hot packs and medicines containing mercury and iodides, the pain and swelling subsided, although a little flexion deformity persisted until the onset of jaundice She had lost 18 pounds in the ten months before the jaundice appeared and was unable to walk more than six blocks, although once a week she drove her car a short distance.

January 6, 1935, laryngitis developed and lasted for a week during which time the patient had a temperature of 99° to 101° F and epigastric tenderness These then disappeared On the morning of January 16 she awakened to notice that her sclerae were jaundiced She had not taken any derivative of cinchophen or other known hepatotoxic drugs and there was no jaundice in the community of which she or her physician knew On discovering jaundice that morning, she was particularly disturbed because she had *planned to* have a party that afternoon and, as she said, "Fixing the house for a party was bad enough with my rheumatism without having jaundice on top of it"

However, as she began to move about she found, to her surprise and delight, that she could perform many tasks that she had been unable to do for many months

"It was a revelation to me," she said, "and that afternoon when friends as usual asked me about my rheumatism I told them it had suddenly left me, for which I was very thankful"

Although the jaundice was painless, her attending physician suspected cholelithiasis or a stone in the common duct on the basis of her experience at the age of eighteen years During the first week the jaundice was noted mostly in the sclerae, and the skin was not very yellow Then the urine became dark, the stools clay colored, and in the second week the skin became intensely yellow and stayed so for two more weeks Fever was not present Itching appeared during the third week of jaundice and has been increasing, although the jaundice has begun to fade somewhat

The patient insists that she has had absolutely no pain or stiffness what

ever since the first day of the jaundice This information was volunteered and was not sought by the physician who first saw her here at the clinic. In the words of her physician who sent her here Her arthritis disappeared through the back door as the jaundice came in the front door"

During the first three days of jaundice she was quite active physically more so than for some time Then her physician advised her to go to bed for a few days since which time she has again been fairly active

On examination at the clinic, February 18 four weeks after the onset of the jaundice icterus grade 2 to 3 was present There was no fever The patient was emaciated, grade 2 and had bradycardia and a pulse rate of 60 The blood pressure was 110 mm of mercury systolic and 0 diastolic The liver and spleen are just palpable The woman always has bruised easily and there are several small ecchymoses over the thighs first noted two weeks ago

All joints appear entirely normal There is no muscular atrophy pathologic shaped swelling residual thickening of periarticular tissues or deformity of joints Full motion is present in all and there is no tenderness or pain on firm pressure on voluntary motion or even on strong passive motion There is slight creaking of both knees There are no Heberden's nodes Roentgenograms of the right knee both ankles and both wrists are negative

The woman has been admitted to the hospital for further investigation The cutaneous temperature of her hand ranges from 29 to 31 C that of the arms from 31 to 33 C that of the feet from 31 to 32 C and that of the legs from 30 to 31.6 C These are approximately within the range of low normal figures The flocculation test is negative Erythrocytes numbered 4,040,000 and leukocytes 6,400 per cubic millimeter of blood the value for hemoglobin is 84 per cent (14.1 gm) The coagulation time is twelve minutes. The value for serum bilirubin on admission was 0 mg per 100 cc the reaction was direct (A normal concentration of serum bilirubin is up to 1.5 mg per 100 cc) The urine contained albumin grade 1 no sugar deposit grade 2 a few granular casts and pus cells A roentgenogram of the region of the gallbladder taken without dye is negative The first duodenal drainage revealed 0 cc of bile stained material present but no B bile All to and laboratory data are given in Table

A diagnosis has been made of inactive chronic infectious arthritis and [illegible] and of jaundice of a type to be discovered

rose to 12 mg again on February 26 Reactions were all direct The pruritus has lessened The liver and spleen are no longer palpable, and purpuric spots have disappeared Stools became dark four days after the woman had been admitted

TABLE 2

SOME OF THE LABORATORY DATA IN CASE III

Examination or substance examined.	Result	Normal
Total lipoids, mg per 100 c.c plasma	947	500 to 550
Total fatty acids, mg per 100 c c plasma	661	335 to 350
Plasma cholesterol, mg per 100 c c.	286	160 to 200
Cholesterol esters, mg per 100 c c. plasma	181	110 to 145
Lecithin, mg per 100 c c plasma	384	200 to 250
Fibrinogen, mg per 100 c c plasma	294	300 to 600 mg
Serum protein, gm per 100 c.c.	4 65 to 6 07	6 to 8
Protein albumin globulin ratio	1 8 1, 1 4 1	1 5 1 to 3 1
Serum sulphates (inorganic), mg per 100 c c	5 9	3 to 5
Stool	Bile present	
Galactose tolerance test	Weakly positive, 3 gm of reducing substance in urine in 5 hours	Less than 3 gm of galactose excreted in 5 hours
Hippuric acid in 24 hour urine	No precipitate, possibly 1 to 3 gm in solution	2 gm in precipitate

to the hospital She feels well and eats well Duodenal drainage revealed material that at first was but slightly bile-tinged, but now clear, amber bile is present Surgical exploration is not advised at present The woman is to return home under the further supervision of her attending physician, and it is

recommended that a diet high in carbohydrates and low in fat be continued, with occasional duodenal drainage as necessary

To me, the main feature of interest however is that the joints have remained entirely free of pain and the woman feels as if she'd never had any rheumatism You see how freely she can move all of the joints, and they do not cause any pain when I press heavily on them and move them forcefully

Comments on diagnosis Dr Hench What type of "rheumatism" did this patient have, which jaundice apparently so successfully has inactivated? With no characteristic roentgenographic changes or alterations in the present appearance of the joints to help us in diagnosis, we must rely on the history in attempting classification The early history suggests that the woman had periarticular fibrositis, so-called capsular rheumatism, associated with localized swellings of tendon sheaths (tenosynovitis) She had fatigue, stiffness soreness of joints but full motion therein, negative roentgenograms, no hydrops, spindle shaped swellings or deformities there was nothing to suggest that the articular cavities themselves were invaded We can probably correctly assume that later the integrity of the joints was assailed as seems obvious from the fact that the knee swelled to twice its normal size This, with the appearance of flexion deformity, suggests more than synovitis, it suggests developing chronic infectious arthritis with accompanying fibrositis

After the initial eight months of periarticular fibrositis the patient enjoyed a gradual remission the customary slow natural remission incident to summer warmth Then after only a month's vacation from pain she experienced more than sixteen months of slowly progressive disability, and then a sudden climactic remission in the activity of the disease not one of the slow incomplete remissions which so frequently produce minor deviations in the condition of an arthritic patient but a sudden overnight remission which we recently have learned to expect of a significant jaundice Previously unable to turn a doorknob squeeze a washcloth or grasp a pen's

with one hand, suddenly this particular morning she is able to do all of these things Thus we see her now with three years' rheumatism inactivated by intercurrent jaundice Dr Snell, will you classify the jaundice for us?

Dr Snell When we saw this patient in the fifth week of her jaundice she was improving fast, and the value for serum bilirubin was dropping from a high to a moderately increased level Although she had some vague abdominal pain at the onset, I do not believe it was from a stone In view of the fact that the jaundice has been painless, the bile ducts are patent and she is improving rapidly, I believe she has had intrahepatic jaundice We cannot be too certain about it, however, but to me, these features suggest intrahepatic jaundice rather than jaundice from obstruction in the common bile duct If she has a stone in the duct, and if she were operated on now she would probably have a stormy time because she has had considerable parenchymatous injury to the liver If it is obstructive jaundice, she can be operated on with more safety later If it is intrahepatic jaundice, it is obviously a condition which is gong to clear up Then her arthritis may return and Dr Hench, not I, will be treating her

A physician What is the significance of her chemical findings other than the bilirubin?

Dr Snell They are not easy to interpret The value for serum protein was definitely low, as it may be in any case of severe hepatic damage, but the serum albumin-globulin ratio was not altered The value for fibrinogen was low, as it often is in the presence of hepatic disease The data on blood fats and cholesterol suggest that biliary obstruction may have been present, as the total lipoids of the blood are twice the normal concentration The difficulty with interpreting all of the above results is that in cases of hepatic disease, values for these constituents of the blood often fluctuate markedly, and do not form curves readily susceptible of analysis

Cholesterol and cholesterol esters are often reduced during a period of intrahepatic jaundice and return to normal or even to high levels as improvement takes place In obstructive

jaundice, high values are the rule but if the liver itself begin to deteriorate the cholesterol may fall to a normal concentration or below

The hippuric acid test is positive as it may be in the presence of almost any type of hepatic disease The weakly positive galactose test also favors the diagnosis of intrahepatic jaundice The excretion of reducing substances may have been greater earlier in the course of the jaundice but as the patient improves the test becomes negative, sometimes even before icterus has disappeared

Dr Hench Some time after this patient's jaundice disappears, the pains, stiffness, and other symptoms referable to her joints probably will return* They may return as the jaundice fades away or they may not return for some weeks or even months thereafter They may return in full force, or in an attenuated form It is not likely that the degree of icterus which she had will be followed by a permanent ameliorative effect, although it would seem from my previous experiences, that such an effect apparently can result in the presence of jaundice that is more severe and more protracted than this patient happened to have

arthritis, fibrositis, and sciatica Coincident generally with the onset of jaundice, fourteen of the sixteen patients received generally complete relief of pain for variable periods, from a few weeks to eight months, in one case for seven years The effect is more than merely an analgesic one, for in several cases in which joints were swollen, reduction of swelling also was noted

Since this report, I have seen in the past year more than a dozen similar cases of arthritis in the jaundiced, pain-free phase and six others in which arthritis, now active again, had been suddenly inactivated for variable periods by intercurrent jaundice experienced prior to the patients' coming here One arthritic patient, jaundiced on two occasions, had noted the same striking analgesic effect both times

All patients discussed in our first report had intrahepatic jaundice In our subsequent cases analgesia has accompanied spontaneous intrahepatic jaundice, infectious, epidemic or catarrhal jaundice, neo-arsphenamine jaundice, cinchophen jaundice, and obstructive jaundice with cholelithiasis Sidel and Abrams have corroborated these findings [16]

A physician What do you believe to be the analgesic agent?

Dr Hench I certainly wish we knew No significant relief is obtained in cases in which the value for serum bilirubin does not eventually reach or exceed 10 mg per 100 c c This seems to be the critical lower level, but since the analgesia occasionally comes on a day or more before visible jaundice appears, and may persist for some time after the value for serum bilirubin has returned to normal, I do not believe bile pigments are responsible In this case you recall that the analgesic effect was noted even before the skin became visibly affected, and when only the sclerae were icteric The serum bilirubin must generally reach a concentration of about 5 to 6 mg before the skin appears jaundiced The beneficial agent may be some other constituent of bile, or an autolysate of liver or of other tissues affected by the jaundice

Dr Snell May I venture an opinion regarding the likely

agent. Since the jaundice in all of these cases has been associated with severe degenerative disease of the liver, I am inclined to think it is some hepatic autolysate, some product of disintegration that enters the blood and produces a nonspecific effect

Dr Hench It may be so, but I personally hope the inactivating agent is something simpler to identify than an hepatic autolysate I express merely a hope that jaundice provides to the general circulation not an abnormal product but a normal constituent, adequate amounts of which perhaps the arthritic patient did not previously have. But this is mere speculation, and studies are under way in an attempt to determine the mechanism whereby the agents act, whether jaundice here provides a bacteriolytic or bacteriostatic effect or a "detoxifying" effect, whether it raises immunity or merely has a sedative effect on nerves and inflamed tissues

A physician Perhaps it is merely a question of counter irritation, the patient who has jaundice is so sick that he doesn't have time to notice his joints particularly while he is in bed, relieving his joints of trauma

Dr Hench I am sure that this is not the correct answer Many of these patients are not particularly sick during their jaundice Indeed a few said they were better than ever and many of them in the absence of pain stiffness, and swelling were not less, but much more active than for some time

the absence of his rheumatism he didn't mind being jaundiced because he could at least scratch

Dr Hench It may be of considerably more than academic interest thus to note that often the rheumatic process apparently cannot continue its activity in the presence of appreciable icterus To me, this observation is a disturbing, but at the same time a stimulating one disturbing because nature seems to be flaunting a possible therapeutic secret in our faces, challenging us to repeat her works, stimulating because, viewing nature's easy victory over a perversely stubborn disease, it suggests that the arthritic process is not as irreversible as might be supposed It suggests that the long, weary journey which many of our patients must today traverse to reach the inactive stage of their disease may not be an inevitable necessity It raises the hope that we too may sometime find the way to score an easy victory if only we can map out nature's short cut

Jaundice is not the only agent which may abruptly provide a more or less complete, if temporary, cessation of rheumatic activity Activity may also cease, for example, through the intervention of pregnancy or of some intercurrent infection But the effect of jaundice is perhaps more concise, and more prompt, and jaundice lends itself somewhat more readily to study and perhaps to therapeutic repetition It is to be hoped that further investigation may lead to the discovery of the responsible agent, and to the use of some nontoxic accompaniment of jaundice, effective in available concentration

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FEVER THERAPY

ARTHUR U DESJARDINS

Of the different forms of physical apparatus thus far designed for fever therapy the one which appeals to me as the most effective from all points of view is the air-conditioned chamber known as the Kettering Hypertherm With this chamber the temperature can be raised more rapidly than with radiant light chambers and any degree of fever can be attained and maintained for as long as the condition of the patient allows or requires Moreover the patient's body (except the head, which is outside) is entirely free within the chamber and the apparatus does not involve the use of contact electrodes condenser plates or other electrical gadgets of any kind The mechanism by which fever is induced consists of a simple air heater to raise the temperature of the air within the chamber, and an equally simple means of humidifying the air to any desired degree The heated and humidified air is then circulated around the patient at the rate of ten times a minute The mechanism is placed in a small compartment at the foot end of the chamber entirely separated from the patient by a substantial partition The temperature of the air is controlled by thermostat and the relative humidity of the air is controlled by a humidistat and by wet and dry bulb thermometric reading With this chamber the patient entire body can be kept under constant observation so that the condition of the skin can be closely watched Moreover the patient's movements are free he is not restricted by confining sickets or anything else and is not burdened by the weight of blanket Also it permits the ready use of the stethoscope

ician to take care of the patient throughout a session of treatment with the greatest ease In case of emergency, also, the chamber can be thrown open and the patient withdrawn in a few seconds All these are advantages which do not exist to the same degree with any other method of fever therapy with which I am acquainted It is possible that later some still simpler and less expensive means of inducing fever may be found For instance, radiant light chambers or inductothermy may be perfected so as to remove the objections which now

Fig 71 —The chamber open with a patient being made ready for a session of treatment

make these forms of treatment less satisfactory than they might be (Figs 71, 72 and 73)

But however simple the means of inducing fever may become, fever therapy is never likely to be an office procedure This is especially true in connection with diseases the treatment of which requires that a high temperature be maintained for hours An essential requirement is that the patient should be kept under constant observation by trained nurse-technicians and that these technicians should be closely supervised by a physician familiar with every phase of the treatment

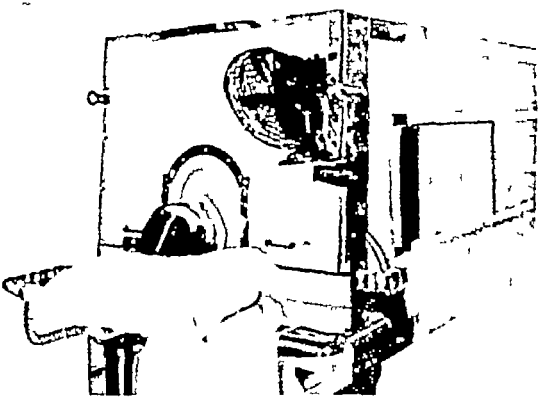

Fig. 2.—The chamber closed and the treatment started. The electric fan blows cool air over the patient's face.

Later it is possible that the lethal temperature of other microorganisms may be found to be within limits that can be duplicated in man If this should prove to be the case, it may become possible to apply fever therapy to conditions such as pneumonia Time alone will tell

Although a few patients were treated by the diathermic method in 1931, our experience with fever therapy at the clinic really dates from December, 1933, when a sound organization was effected Since then we have treated 200* patients, who have received 1,033 sessions of fever Of these, fifty-six patients have been treated for acute or chronic gonococcal urethritis, with or without complications including arthritis and salpingitis, and have received 289 sessions of fever, or an average of five sessions Between December, 1933 and December, 1934, thirty-three patients were treated Four cases must be excluded because the patients did not return after the first session of fever or because they failed to cooperate and the idea of treating them had to be abandoned Of the twenty-nine remaining patients, twenty-five received systematic treatment and were cured The urethral discharge ceased, all symptoms disappeared, and the patients have been well since the treatment was completed The average number of sessions of fever required to effect a cure was 5 4 One patient required twelve sessions, one required ten sessions, and one required seven sessions of treatment before the gonococcic infection was cured This was because, during the early sessions, an adequate degree of fever could not be attained or could not be maintained long enough The lowest number of sessions of fever required for cure in any case was three

Four patients, all females, were not cured, probably because the required degree of temperature could not be attained or consistently maintained for a sufficient time

In treating gonococcic infections the aim is to destroy the infecting organism directly by subjecting it to a sufficiently high temperature for a sufficient length of time Both factors are equally important As Carpenter, Boak, Mucci and Warren

* Until March 1, 1935

have shown, some strains of gonococcus can withstand a higher degree of heat, or can withstand the same degree of heat for a longer time than others

During the early phase of this work the sessions of fever were repeated only when the urethral discharge reappeared that is, after a lapse of from three to seven days Later, only two days were allowed to intervene between sessions At first, also, a rectal temperature between 41 1° C (106° F) and 41 7° C (107° F) was maintained for five hours in most cases, but in some cases such a degree of fever was not attained or it was not consistently maintained for five hours This explains why a few patients required as many as seven teen and in one case even twelve sessions of fever to effect a cure Now, the first two sessions are regarded as test sessions, and a temperature between 41 1 C (106° F) and 41 7° C (107° F) is maintained for six hours If by that time the urethral discharge continues and gonococci are still found in smears or by culture, the duration of subsequent sessions is increased to seven or eight hours With such a scheme of treatment, more than four sessions of treatment should seldom be required

Well-controlled diabetes does not contraindicate fever therapy for gonococcic infection or for any other condition for which fever therapy may be indicated One of the patients treated and cured belonged in this category He tolerated treatment about as well as other patients

The rapidity with which the swelling and pain associated with gonococcic arthritis subsides during and after the first session of fever is astonishing In cases in which the articular inflammation is acute the effect of fever therapy is really spectacular In most cases thorough treatment is followed by complete and permanent resolution of the inflammatory process When the inflammation is chronic active inflammation and the accompanying symptoms abate and disappear but reparative changes in the form of connective tissue proliferation deposition of bone as well as the resulting disturbance of function are not influenced In some cases of acute and

pingitis yields promptly and completely, but our experience of treatment for this complication has not yet been sufficient to enable us to know to what extent secondary infection may diminish the effectiveness of fever therapy in such cases

CHRONIC ARTHRITIS

Patients suffering from hypertrophic (senescent) arthritis do not derive substantial benefit, as a rule The condition of a small proportion improves to a limited degree, but the majority obtain little or no improvement In chronic infectious (atrophic) arthritis, about a third of the patients are greatly benefited, a third derive moderate benefit, and a third obtain little or no relief

Whatever the form of arthritis may be and whatever the degree of relief which the patient may obtain from fever therapy, the treatment cannot be expected to correct deformity and impairment of function due to organization of inflammatory infiltrates and to reparative processes accompanied by proliferation of connective tissue By eliminating from consideration a considerable proportion of the patients suffering from chronic hypertrophic arthritis, and perhaps some of those afflicted with chronic infectious arthritis, and concentrating on the remainder, a better showing could be made But only time, prolonged study, and greater knowledge of arthritis will enable one to select suitable cases with a greater degree of assurance than is now possible

OTHER CONDITIONS

Among the other pathologic conditions in which fever therapy has been tried, may be mentioned syphilis of the nervous system, chorea of children, asthma, multiple sclerosis, and scleroderma Of syphilis of the nervous system we have had an opportunity to treat only a limited number of cases Nearly all of the patients had been treated by other methods for a time, many had received previous treatment with malaria, to which they did not respond favorably or which, after a period of improvement followed by recurrence of symptoms, no longer had a favorable influence A much larger

number of patients will have to be treated and a number of years must elapse before we can evaluate fever therapy in comparison with other methods.

In the nine cases of chorea in children who have been treated all have improved satisfactorily but greater experience will be required to give us a correct perspective on the value of artificial fever in comparison with other methods of treatment. Moreover, the possible influence of artificial fever on subsequent attacks must remain indefinite for some time. One thing seems certain. If the therapeutic value of injecting vaccine prepared from paratyphoid or other micro-organisms depends on the fever thereby induced the induction of fever by an efficient physical method should make for improved results, because the fever can be effectively regulated. Another advantage of fever induced by physical means is that, by eliminating the toxic factor the fever is not preceded or accompanied by chills, and to this extent the discomfort of the patient is considerably diminished.

Of asthma, the few cases in which fever therapy has thus far been tried have been chiefly those in which the patients had not been benefited by ordinary methods of treatment. Nevertheless, some of them have improved. Only it is not yet possible to say how long such improvement may continue. A few cases of scleroderma have been subjected to a number of sessions of fever without strikingly favorable results. The condition of one patient improved for a time but it seems doubtful if the improvement will be maintained.

eight or more hours Therefore, the lethal temperature and the time during which it is maintained are the two main factors, if not the only factors in the influence of fever

The improvement often observed in infectious processes caused by other bacteria must be explained on other grounds

Fever is known to produce the following changes

Increased flow of blood (hyperemia) whereby the temperature of different parts of the body is roughly equalized and whereby the heat is brought to the surface for dissipation through the skin

Increased action of sweat glands to help in dissipating the heat A patient may lose several pounds of sweat during a session of fever

Increased rate of respiration to help in dissipating the heat

General increase in metabolism (about 8 per cent for each degree of temperature)

Increase in the number of leukocytes, especially of the polymorphonuclear cells This varies considerably with different patients, sometimes the increase is slight and sometimes the number of leukocytes may double in five hours The number of cells returns to normal in about twenty-four hours

Increase in sedimentation rate

Other changes which may occur, but undisputed proof of which is not yet available

Increased phagocytosis

Increased formation of antibodies

TECHNICAL CONSIDERATIONS

In general, the treatment is tolerated quite well The absence of any toxic factor and of the resulting chills removes an important factor in the discomfort associated with a high degree of natural fever Few patients become delirious at any time A certain degree of excitement may accompany a high fever in many cases, but true delirium is seldom observed The manner in which a patient accepts the treatment, and behaves during treatment, is an accurate index of the character and temperament of the individual The poised person,

who is determined to get well behaves accordingly Some patients hum, sing, chat, or smoke throughout a session of fever maintained between 106 and 107° F Some remain quiet and sleep much of the time Others ask to be released from the chamber long before the session is scheduled to end Nervous individuals, persons without fortitude or who have never known the meaning of self-control are prone to fuss more or less Of course, this depends largely on the degree of fever

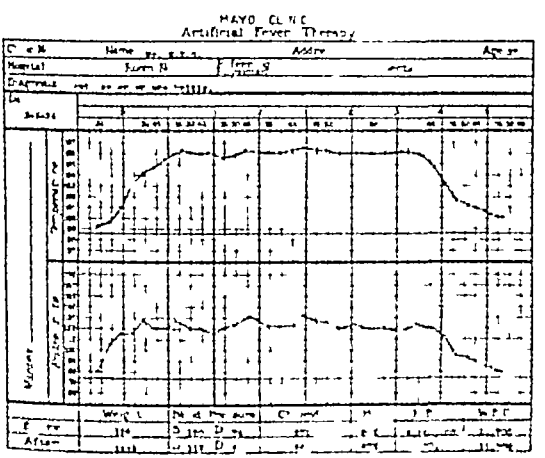

Fig 1—Chart of temperature and pulse rate during a session of fever maintained between 106 and 107 F for a neurosyphilitic

which may seriously interfere with an adequate intake of fluids and chloride during treatment Loss of weight from abundant perspiration, and loss of strength from excessive excretion of chlorides through the skin, are prevented by causing patients to drink from 2 to 5 liters of a 0 6 per cent solution of sodium chloride during each session of treatment As a result, the weight of the average patient actually increases, and the weakness disappears within twelve or twenty-four hours

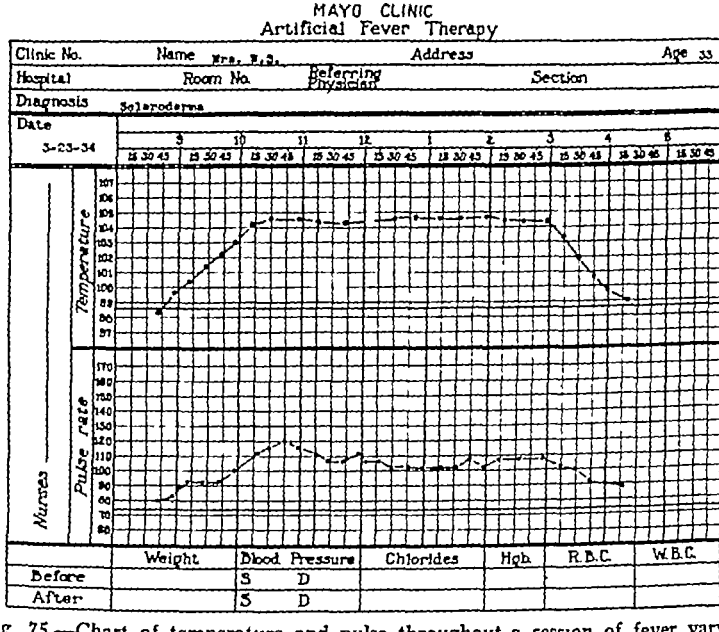

Fig 75 —Chart of temperature and pulse throughout a session of fever varying between 104.5° and 105.5° F for chronic infectious arthritis

When a patient loses weight during treatment, it is because, for some reason, he does not or cannot take a sufficient quantity of chloride solution, this happens occasionally (Figs 74, 75)

Patients enter the chamber without breakfast and do not take food until sometime after the session has terminated and their temperature has returned to normal Then they are given milk and encouraged to take more milk frequently for twenty-four hours At the outset, the rectal temperature is

taken every ten minutes, but after the temperature has risen to 104 F it is taken and recorded every five minutes

Fever therapy is a fairly strenuous cardiovascular test Therefore, patients of more than sixty years of age, or patients of any age who may be suffering from cardiac or renal disturbances, should not be subjected to it Occasionally, the age limitation may be disregarded, but only when the condition of the cardiovascular apparatus has been carefully ascertained

The treatment should be conducted by carefully selected and specially trained nurse-technicians who are not allowed to leave the patient until the session of fever has been completed and until the patient's temperature has returned to normal Moreover, the technicians should be under the constant supervision of a physician who is familiar with all phases of the method If a technician must absent herself momentarily, her place is taken by another technician or by the supervising physician Lunch is brought to them and is eaten in the service

Under such conditions, and if the patients are carefully selected, only minor complications are likely to be observed These include herpes around the lips and mouth occasional blisters in skins that are unusually sensitive and that are slow to adapt themselves to a rapid rise in temperature and muscular tetany, usually confined to the hands and feet but which may sometimes affect other groups of muscles This is an uncommon disturbance, apparently results from overventilation and disappears almost instantly on administration of carbon dioxide and oxygen, it often abates just as promptly on intravenous injection of 10 c c of calcium gluconate

Fever therapy, especially for conditions requiring a high temperature, should be conducted in an institution where adequate facilities and trained personnel can be organized into an effective team It cannot be carried out in conjunction with other medical practice without increased risk

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ROENTGEN THERAPY FOR INFLAMMATORY AND MALIGNANT CONDITIONS

EUGENE T LEDDY

It may seem paradoxical that roentgenotherapy and radium therapy should give favorable results in the treatment of inflammatory and infectious diseases particularly since it is well known that bacteria in the tissues or in culture are extremely resistant to radiation, even when maximal doses are employed The explanation for the benefits which are obtained with radiotherapy is that the cells that make up the pathologic lesion are sensitive to roentgen rays Abundant clinical and experimental evidence has been produced to

are similar to antibodies, are destroyed by the radiation and the defensive substances are released in larger amounts than they are normally and tend to overcome or arrest the infection Roentgenotherapy, when correctly applied, commonly aborts infections, especially if it is administered before actual suppuration has taken place If actual suppuration has occurred, the liquefied portion of the lesion should be aspirated before irradiation is employed Roentgenotherapy may hasten resolution and relieve the pain even in cases in which frank suppuration has occurred I might emphasize the fact that in the treatment of acute inflammation small or moderate doses should be administered early and that the dose should never approach anything like the intensity of that which is employed in the treatment of malignant conditions, and that injury to normal structures should never be permitted to occur

Any discussion of roentgenotherapy of malignant tumors is controversial, not only is the field a comparatively new one, but the actual technic often is individual to the radiotherapeutist. It is a fact, I think, that all the different types of cells in the body have a specific sensitivity to roentgen rays I mean that the same type of cells have the same degree of sensitivity to roentgen rays and that different types of cells, as lymphocytes and epithelial cells, will each react in a different manner It therefore is possible to predict the manner in which a tumor, the microscopic structure of which is known, ought to react On the other hand, the reaction of a tumor to irradiation frequently furnishes valuable information about the type of the lesion in cases in which biopsy has not been performed Other things which are of great value in outlining the dose of radiation are the condition of the patient and the type of operation that has been, or is to be, done Whether a tumor is graded 1 or 4 will often enable the roentgenotherapeutist to determine the intensity, frequency, the extent of the irradiation and the extent of the body to treat

The technic depends on the cellular structure of the lesion Tumors, of course, are composed of abnormal cells The radiosensitivity of tumor cells resembles that of the normal

cells from which they are derived The cells which are proliferating actively are more sensitive than are normal cells A tumor that is derived from normal tissue that is radiosensitive, will be radiosensitive, but if it is derived from tissue cells that are resistant to irradiation, the tumor also will be resistant Knowledge of radiosensitivity of the tissues of the body has been developed to a high degree It is known, for instance, that blood cells are extremely sensitive to radiation, and that lymphocytes and leukocytes are by far the most sensitive cells It therefore becomes evident that leukemia and lymphoblastoma to mention two diseases of the hemato poietic system, are responsive to radiotherapy In this group of diseases, leukemia and lymphoblastoma respond to light doses The response is rapid, oftentimes spectacular and the disease usually regresses satisfactorily both to the patient and to the physician Unfortunately, these diseases have a tendency to recur after a period of remission and the ultimate prognosis is always fatal

Among the other tumors which are usually radiosensitive, are tumors of the testis These tumors are commonly radiosensitive because the normal spermatogenic cells from which they are derived are radiosensitive If they are composed of adult cells of the differentiated type such as the cells of teratomas or of true carcinoma the response is less satisfactory and less nearly complete than it is in rapidly growing, immature cells which make up the most common tumor, the

to roentgen rays Because of the high price and scarcity of radium which is the natural source of gamma rays, the problem of building a machine to produce these rays artificially has arisen It is too early to draw any conclusions about the value of these machines or of the "super high-power" roentgenologic hook-ups In general, it can be said that all squamous cell carcinomas should be treated by combined roentgenotherapeutic methods and that no one method should be adopted to the exclusion of the others Squamous-cell carcinomas of the esophagus and most carcinomas of the gastro-intestinal and genito-urinary tracts can be handled either by roentgen rays or radium, but, at present, a lasting favorable result is the exception rather than the rule Palliation generally is all that can be accomplished

There has been definite progress in the field of carcinoma of the rectum Many operable lesions have been arrested by radium and without operation

The second great group of carcinomas consists of the glandular type of carcinoma Normal glandular tissue is sensitive to radiation and for this reason carcinomas of glandular tissue are no exception to the rule Perhaps the most sensitive of them all is carcinoma of the thyroid gland The sensitiveness of this tumor to roentgen rays and radium approaches that of lymphoblastoma, which is one of the most sensitive tumors Carcinoma of the thyroid gland, which is rarely diagnosed before operation, is most satisfactorily treated with a combination of excision of the tumor and postoperative roentgenotherapy of the neck, or of any part of the body to which the tumor has metastasized Metastasis from a carcinoma of the thyroid gland is generally an exception to the rule that metastatic lesions do not respond well to roentgenotherapy If there is metastasis to the lungs or bones, a palliative result can often be produced by roentgen rays Glandular carcinomas of the gastro-intestinal tract resemble the squamous-cell carcinomas in their reactions and are a rather poor field for radiation At present, because of technical difficulties inherent in their treatment, I think that all carcinomas of the gastro-

intestinal tract, with the exception of an occasional carcinoma of the rectum, should be treated surgically

In the treatment of tumors of the kidney, the value of roentgenotherapy is more or less unsettled There are two rather different types of tumors of the kidney to consider The first is embryonal carcinoma This type is most common among children, but occasionally may affect adults It is characterized by its radiosensitivity, following light doses of radiation, it may disappear This response distinguishes this type from other tumors of the kidneys It seems to be the consensus of opinion that this group of tumors is best handled by a combination of excision of the tumor and preoperative and postoperative roentgenotherapy In other types of tumors of the kidney, the place of roentgenotherapy is less certain Whether it is better to excise the tumor immediately on diagnosis and to employ postoperative roentgenotherapy, or to use preoperative roentgenotherapy, surgical treatment and postoperative roentgen treatment is an open question

Normally, connective tissue is rather resistant to roentgenotherapy and it takes intensive doses to produce changes in it Tumors such as fibrosarcomas, chondrosarcomas, and myxosarcomas, which are derived from connective tissue, are, as a whole, resistant to roentgenotherapy

radiotherapeutist is the fact that the tumor will not metastasize and will result in only local disability However, it must be remembered that it is extremely difficult, if not impossible, in many cases, to differentiate between benign giant-cell tumors and malignant sarcomas Only by surgical exploration of the tumor and biopsy can the diagnosis be made and the correct treatment instituted The second exception to the statement that tumors of bone are resistant to roentgen rays is Ewing's tumor This tumor is characterized by its sensitivity to roentgen rays, and a favorable regression can frequently be obtained from rather mild doses of roentgen rays This characteristic sensitiveness to roentgen rays has made it possible to distinguish, without microscopic examination, between Ewing's tumor and other lesions of bone which resemble it clinically and roentgenologically For example, the degree of reaction is used to distinguish between a periosteal tumor and Ewing's tumor in obscure cases Oftentimes, the brilliant results of roentgenotherapy are nullified by distant metastasis

At the head of the list of resistant tumors are those of the nervous system Tumors derived from nerve tissue are generally resistant to roentgenotherapy, however, some of them, particularly those which are made up of highly undifferentiated cells, respond favorably

I would like to emphasize that it is a grave mistake to treat an inflammation with a "carcinoma dose" of roentgen rays The lesions are fundamentally different Carcinoma is malignant and is resistant to roentgen rays, inflammation is benign and sensitive to the roentgen rays Therefore, to apply the same treatment to both is obviously nonsense Furthermore, in carrying out careful treatment of inflammations, the risk of producing lasting or serious changes in normal tissues is negligible Both forms of disease should be treated by a technic, which has been worked out carefully, and the dose that is to be used should be decided on with great precision and care Hit or miss treatments are extremely dangerous procedures It smacks of quackery to attempt to treat a deep-seated carcinoma of the uterus with low-power diagnostic

roentgen rays But such things are done In treating any form of lesion, one should not lose sight of the fact that every roentgenologic treatment produces some damage, that the magnitude of the damage is the magnitude of the dose, and that inattention to the details of treatment or to the actual administration of the roentgen rays may result in a worse condition than existed before the treatment was administered It is necessary to remember that even though a lesion cannot be treated from the outside with roentgenotherapy, a deep-seated tumor often can be satisfactorily treated from the inside with radium Radium can thus produce an effect that roentgen rays cannot

In general, radiotherapy should be carried out by a combined method of treatment Instead of drawing a sharp line of distinction between roentgenotherapy and surgical treatment, they should overlap In considering the treatment of a lesion particularly carcinoma, one had best rely on the combined opinions of the surgeon, the roentgenologist, and the radium therapeutist

Medical Clinics of North America
September 1915 Mayo Clinic Number

EPITHELIOMAS OF THE ARM SIMULATING ENDOTHELIOMA, SARCOMA, AND SPOROTRICHOSIS TWO UNUSUAL CASES

HAMILTON MONTGOMERY

The two cases here to be reported were not recognized clinically as instances of epithelioma of the arm They represent, I believe, an uncommon, but not rare, type of epithelioma of the extremities Many such lesions have been confused with sarcomas and so-called endotheliomas of the skin, to say nothing of sporotrichosis and other granulomas of the skin

REPORTS OF CASES

Case I.—A woman aged twenty years was seen in The Mayo Clinic February 19 1915 because of cutaneous lesions of seven years duration She

right forearm, on the ventral surface, these had opened spontaneously and serous material had been discharged Roentgenograms had failed to give evidence of involvement of bone, and a specimen taken for biopsy had been of indeterminate characteristics Each time after incision the ulcers had healed, then they had grown more rapidly and had broken down again

Examination revealed lesions such as are represented in Fig 76 There was also a large axillary node The clinical appearance of the lesions was suggestive of endothelioma or sarcoma Sporotrichosis and tuberculosis were considered in differential diagnosis Specimens taken for biopsy revealed squamous-cell epithelioma, grade 3, simulating both endothelioma and sarcoma in histologic appearance Further sections, however, revealed areas where there was definite pearl formation, and where there could be no question as to the epithelial nature of the tumor cells The arm was amputated at the shoulder, and the axillary lymph nodes were cleanly resected, in the nodes, also, tissue of squamous-cell epithelioma, grade 3, was found The patient died in November, 1930 Postmortem examination was not performed

Case II —A furniture mover, aged twenty-nine years, was first examined in the clinic August 7, 1933, because of cutaneous lesions such as are represented in Fig 77 In January, 1930, the patient had noticed a rather sensitive, hard, subcutaneous nodule, the size of a pea (about 1 cm in diameter) on the anterior aspect of the left arm This gradually had increased in size until it had been about 5 cm in diameter A surgeon had made a diagnosis of malignancy in December, 1931, and had excised the nodule At the same time, the axillary lymph nodes, and some of the muscles of the arm, had been resected The diagnosis of one pathologist had been epithelioma, and of another, sarcoma The patient had received six or seven roentgenologic treatments, each of half an hour's duration The operative wounds had healed Five months after the operation, multiple ulcers had formed on the left arm, shoulder, and upper portion of the left side of the thorax He had been given daily roentgenologic treatments, each of half an hour's duration, for sixteen days, but because the ulcers had failed to heal, they had been treated with the electric needle in October, 1932, and this had been followed by skin grafting The ulcers then had healed, but had recurred in January, 1933, and had been removed surgically However, new ulcers had formed About five months before the patient came to the clinic, he had noticed a lesion on the upper, left eyelid, which had increased in size until it was 6 cm in diameter The patient had been presented at a dermatologic meeting in June, 1933 Diagnoses of factitial or feigned eruption, and also of endothelioma had been considered The suspicion of feigned eruption was increased by the presence of corneal and pharyngeal anesthesia

The patient gave a history of having had a cough and night sweats for the past year, and occasional blood-streaked sputum but no hemoptysis His weight at the time of examination was 155 pounds (70.3 kg), his normal weight was 164 pounds (74 4 kg) He tended to attribute the recurrence partly to trauma incident to his occupation as furniture mover He subsequently stated that several cousins and aunts in his family had cancer of the skin or internal organs, and that his grandfather had died of cancer

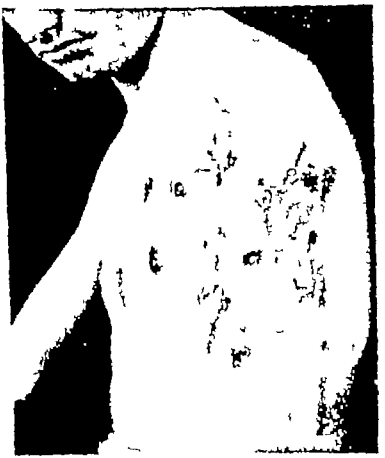
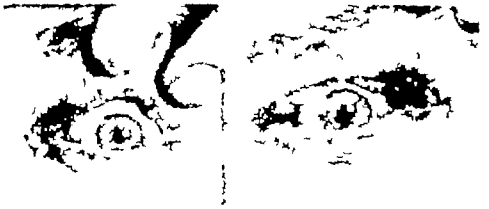


Fig. Case II. Squamous cell epithelioma grade 4. Rolling of the borders of some of the ulcers is conspicuous. Scars are results of previous operation.



obstruction that presumably was the sequel of resection of the axillary lymph nodes The lesion of the upper eyelid (Fig 78, *a*) suggested clinically a basal cell epithelioma A specimen taken for biopsy, from one of the ulcers of the arm, disclosed a squamous-cell epithelioma, grade 4, simulating the picture of fibrosarcoma (Fig 79) Specimens subsequently taken for biopsy, from metastatic lesions on the thorax, eye, and scalp, were all consistently squamous

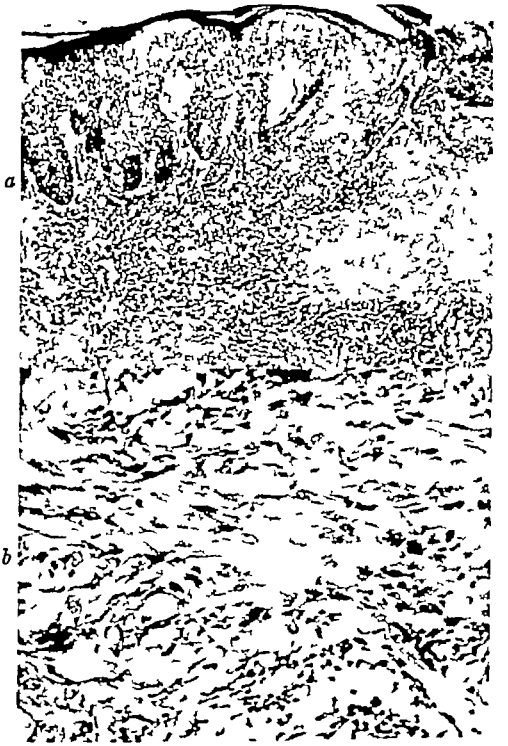


Fig 79—Case II *a*, Squamous-cell epithelioma, grade 4, from specimen from arm Necrosis and fibrous-like arrangement of tumor cells beneath the epidermis can be noted, also, origin from the epidermis at the edge of the ulceration, *b*, higher magnification of *a* Malignant epidermal cells simulate connective tissue cells, numerous atypical mitotic figures are present

cell epithelioma grade 4 Several of the metastatic growths revealed areas more typical of undifferentiated squamous cell growth From roentgenograms of the thorax a diagnosis of chronic bronchiectasis was made, although metastatic growths could not be excluded Several specimens of sputum were negative for bacilli of tuberculosis Because weight had not been lost, and because definite evidence of metastasis to the thorax was absent, radical amputation of the arm, shoulder, and entire scapula, as well as of half of the

clavicle was performed by Dr Ghormley The wound healed satisfactorily Radium was applied to the lesion on the eye and there was partial involution at first but further intensive treatment with radium was without avail (Fig 8 *b*)

The patient was seen frequently for about a year In the interval between operation and September 1 1934 several new lesions appeared on the scalp and at the operative site or some distance from the operative scar At the time of his last visit subcutaneous nodules could be felt in the right forearm One lesion on the scalp which was treated by extensive cautery resection recurred in four months Another ulcer on the scalp proved resistant to large doses of radium Repeated roentgenograms of the thorax, and consultation with several internists left the question open as to whether the patient had multiple chronic bronchiectasis or whether he had metastatic lesions in the thorax The latter never could be definitely proved At the time he was last seen at the clinic there was still no evidence of any loss of weight In the autumn of 1933 the man had an attack of pneumonia but regained his weight after this He died at home October 15 1934 some four years and nine months after the onset of the trouble and about three years after the first operation had been done elsewhere His physician at his home stated that postmortem examination had not been performed but that in the last months of his life new nodules had developed on the thoracic wall and that toward the end his dyspnea had become very marked In the home physician's opinion there was certain evidence of metastasis to the lungs, as well as of bronchiectasis

except in metastatic lesions These cases present a definite clinical picture which is usually confused clinically with that of sarcoma, sporotrichosis, tuberculosis, syphilis, and other granulomas of the skin Taking of a specimen for biopsy and histopathologic study is definitely indicated to determine the correct diagnosis

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Medical Clinics of North America
September, 1935 Mayo Clinic Number

UNUSUAL CUTANEOUS TUBERCULOSIS (HEMATOGENOUS IN TYPE) PROVED BY DEMONSTRATION OF BACILLI OF TUBERCULOSIS IN THE SKIN

HAMILTON MONTGOMERY

but no expectoration There had been slight hemoptysis on several occasions, and also some loss of weight and anorexia The patient gave a history of having had inflammatory rheumatism eight years previously, with swelling and soreness of the knees, wrists, and shoulders Several specimens of sputum had been negative for bacilli of tuberculosis

General examination in the clinic revealed hypertrophic arthritis of both hips, infiltration of the right hilus at the third and fourth interspaces, and a few coarse râles Roentgenograms gave evidence of a small region of dense infiltration in the right hilus, and a small cavity in the second interspace Secondary anemia was present Bronchoscopy was performed on two occasions The second time, a piece of tissue was removed from a rather firm portion The pathologist reported it as very inflammatory tissue

The patient went home, but returned to the clinic September 16, 1927, chiefly for another general examination At that time, roentgenograms of the lungs were negative A large mass had developed in the right groin There were several nodules in the scalp, especially in the right temporal region Several clinicians suspected the possibility of malignancy, possibly of metastasis from carcinoma of the lung, or even sarcoma There was now definite

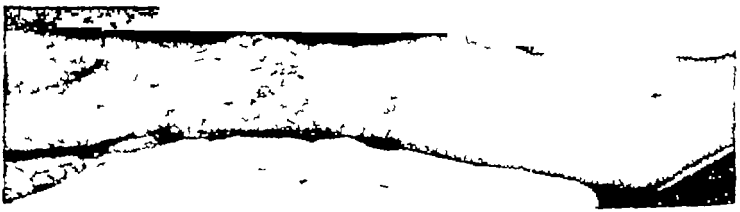

Fig 80—Case I Multiple subcutaneous abscesses of right arm

secondary anemia, the value for hemoglobin was 42 per cent, erythrocytes numbered 4,230,000 and leukocytes 12,500 per cubic millimeter of blood The patient was hospitalized for further study The mass in the groin was found to be an abscess, which was drained The patient began to run a rather septic temperature, which averaged between 99° and 102° F, most often between 100° and 101° F Various blood cultures gave negative results Subsequent roentgenographic examinations of the chest were all negative The agglutination for Brucella melitensis, variety abortus, was negative The Wassermann test for syphilis was negative Further subcutaneous abscesses developed on different parts of the body The abscesses would begin as indurated nodules and after six or eight weeks would break down to form fluctuant masses, but without coming to a head or without the skin becoming erythematous A specimen of tissue was removed from the arm in November, 1927, and at first was thought to have undergone inflammatory changes but later the diagnosis was changed to tuberculosis Osteomyelitis developed in the right temporal region as the result of an abscess beneath the right temporal muscle A small specimen was removed for biopsy on December 6, 1927, and evidence of tuberculosis was found

During all this time the patient was running a rather high fever but he was not having chills or sweats The question of the presence of systemic blastomycosis was considered and by the middle of December the general character and distribution of the subcutaneous abscesses (Fig 80) closely simulated that in the case which I reported in Medical Clinics of North America In fact both dermatologists and internists strongly favored this diagnosis so that the patient was transferred to the dermatologic service Smears and cultures for blastomyces actinomyces and other fungi however gave negative results Also specimens taken for biopsy all showed the microscopic picture of tuberculosis especially that of scrofuloderma (tuberculosis cutis colliquativa) and none of the histologic features of blastomycosis After a good many slides had been searched for bacilli of tuberculosis it was possible to demonstrate two acid fast organisms in epithelioid cells of the first specimen taken from the arm These organisms presented all the morphologic features of bacilli of tuberculosis Meanwhile material from the right forearm had been injected into two guinea pigs both of which died two months later and postmortem examination revealed miliary tuberculosis of the spleen liver and peritoneum Roentgenograms of the thorax December 19 disclosed a slight infiltration of the left lung enlargement of the heart caudad and a thickened left pleura Roentgenograms of the ankles knees wrists and elbows were negative those

of having had a typical attack of erythema nodosum of three weeks' duration, the lesions of which had practically finished undergoing involution In November, 1929, she was in an automobile accident and suffered a fracture of the right clavicle, at which time lesions were first noticed on the skin Further questioning elicited the information that a year after the attack of erythema nodosum, lesions which were regarded as freckles appeared on the

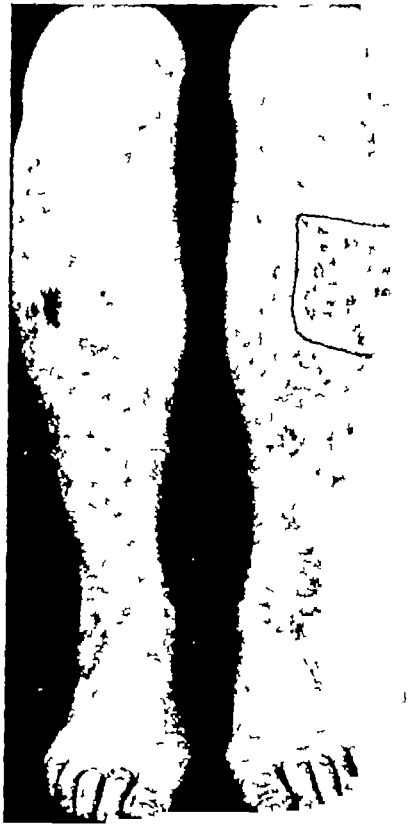

Fig 81—Case II Tuberculosis cutis follicularis disseminatus, general distribution of lesions

legs, but the patient was struck by their unusual distribution She did not think that new lesions had kept appearing, although some of them had changed in color from time to time Examination revealed multiple, discrete, macular lesions distributed over the lower part of the legs (Fig 81, 82), some with a fine, adherent scale and others having a silvery flaky scale, most of them were brownish and displayed a certain degree of telangiectasia The diagnosis of Schamberg's disease was favored, although purpura simplex and parapsori

pressed There was a tendency toward grouping of the lesions The patient was presented to visiting dermatologists who concurred in the diagnosis of lupus miliaris disseminatus Nasal smears and specimens of sputum were negative for bacilli of tuberculosis

The patient returned in December, 1929, for further study, at which time another lesion was excised from the leg for inoculation of brain broth and for injection of a guinea-pig Direct examination of this papule failed to reveal Mycobacterium tuberculosis, and guinea-pigs inoculated with the material subsequently proved negative for demonstration of tuberculosis The patient received a course of twenty injections of gold sodium thiosulphate There was perhaps slight improvement, the lesions becoming a little more superficial at the end of the course of treatment Two months later, there was very definite improvement, so that the patient had only pigmented, telangiectatic,

Fig 83 —Case II *a*, Typical epithelioid tubercle formation with early caseation *b*, Tubercle formation relation to hair follicle, with marked central caseation necrosis

atrophic areas which Dr Goeckerman pointed out could be readily mistaken for Majocchi's disease (purpura annularis telangiectasis)

In January, 1931, the lesions were entirely cleared except for superficial scars, but two years later two pigmented areas and petechiæ appeared The patient was afraid that recurrence was beginning Biopsy of one of the lesions revealed a picture of early verruca senilis Biopsy of a second lesion on the leg disclosed collections of epithelioid cells with occasional giant cells about the blood vessels in the vicinity of the sweat ducts Stains for bacilli of tuberculosis were negative The site from which the lesion of verruca senilis had been removed by punch biopsy failed to heal, and a serosanguineous fluid continued to exude for several months in spite of various types of local treatment cautery and pressure bandages A few superficial varicose veins near the site were injected Healing finally occurred five months later, but it was difficult to explain on what basis this persistent serous discharge had occurred

When the patient was last seen in February 1934 there had been no recurrence of the lesions. The skin of the legs was entirely free of lesions except for the scars at the sites from which specimens for biopsy had been removed

COMMENT

Case I represents a most unusual instance of cutaneous tuberculosis simulating the picture of systemic blastomycosis,[7] and probably originating from a tuberculous abscess of the lung It emphasizes the value, in diagnosis, of taking specimens for biopsy and histopathologic study Bacilli of tuberculosis were demonstrated only with difficulty in the histologic material Diagnosis was confirmed by positive inoculation of guinea pigs Because of the generalized distribution of the abscesses, the case should be classified with the hematogenous forms of tuberculosis, in spite of the clinical and histopathologic resemblance to scrofuloderma (tuberculosis cutis colliquativa) of the individual lesions

unusual to be able to demonstrate bacilli of tuberculosis in such a benign type of tuberculosis as was present in this case, and especially in an area where the histologic response was essentially that of an epithelioid tubercle, as is seen in sarcoids The acid-fast bacilli in this case presented all the morphologic features of bacilli of tuberculosis Careful control of the staining reactions excluded, I believe, a false interpretation of pseudo-acid-fast organisms That inoculation of guinea-pigs gave negative results would not deny the correctness of the diagnosis, but most probably would indicate that a suitable lesion had not been excised for inoculation into the animals, for it is well known that epithelioid tubercles rarely contain demonstrable organisms, nor, as a rule, can positive results with guinea-pigs be obtained from inoculation of material from such epithelioid tubercles of the skin

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Medical Clinics of North America
September 1945 Mayo Clinic Number

COOPERATIVE MANAGEMENT IN CASES OF CARCINOMA OF THE COLON THE INTERNIST'S VIEW

J ARNOLD BARGE

Roentgenologic examination is rarely required in cases in which a neoplasm of the colon has been discovered by digital examination If roentgenologic examination is necessary, a barium enema should be employed instead of a barium meal The latter is likely to cause intestinal obstruction, which not only increases the operative risk but sometimes necessitates an emergency operation

By the cooperative management of patients, in which surgeon and internist work together, patients who have organic

which is made from the bacteria that commonly are found in the peritoneal cavities of patients who have died with peritonitis The incidence of peritonitis has been greatly reduced by this measure The vaccine contains streptococci and Escherichia coli, about 1,000,000 bacteria per cubic centimeter of which 0 5 to 1 c c with 10 c c of physiologic saline solution is injected into the peritoneal cavity, with aseptic technic This is done about forty-eight to seventy-two hours before the operation The reason that it is injected at this time is because it has been found that the normal cell count of the peritoneal cavity of man is around 4,000 cells per cubic millimeter, and most of these cells are lymphocytes Twenty-four hours after the injection there are fourteen times as many cells as there were before, these cells are chiefly polymorphonuclear neutrophils Forty-eight hours later the polymorphonuclear neutrophils are replaced by large monocytes The cellular influx is at its height between forty-eight and seventy-two hours after the injection, or at the time of the operation On the evening before the operation some sedative is administered, and the nurse is instructed to insert a catheter into the rectum and aspirate any residual intestinal content Just before operation this is repeated

Our aim is to send the patient to the surgeon with an empty and dry bowel After operation the cooperative management is continued

Medical Clinics of North America
September 1935 Mayo Clinic Number

COOPERATIVE MANAGEMENT IN CASES OF CARCINOMA OF THE COLON THE PROCTOLOGIST'S VIEW

LOUIS A BUIE

When a patient registers at The Mayo Clinic he is referred to one of the general diagnostic sections for a diagnosis In the course of such an investigation if the patient reveals that there has been any departure from normal intestinal function, he is sent to the section on proctology for examination of the anus, rectum and sigmoid Among the most significant symptoms which we should consider as indicative of intestinal derangement are constipation, frequent stool pain and bleeding Bleeding is most significant One would hardly expect to find a patient who has a carcinoma of the rectum or sigmoid and who has not passed blood However, it is possible for a carcinoma of the rectum to exist without blood having been passed It is necessary for a rectal carcinoma to break through the mucous membrane of the bowel before bleeding occurs and it is doubtful if a lesion would produce symptoms which would call the patient's attention to it previous to its breaking through I have discovered carcinoma in cases in which the patients gave negative history of bleeding, but on those occasions the lesion was discovered accidentally in connection with a general examination Many polyps are found in the same It is assumed that a carcinoma of the rectum will not bleed until it has broken through the mucous membrane and when such a growth has broken through it should be regarded as somewhat beyond what is properly considered

be masked in the form of a troublesome frequency caused by an annular, obstructive, malignant lesion of the sigmoid It is, therefore, much safer to assume that a patient has a carcinoma until it is possible to prove that one does not exist

Pain is a significant symptom, but one does not always find it easy to determine the true character and significance of this symptom from the statements given by the patient There are several types of pain which are very definite and which always can be interpreted as being attributable to anal or rectal disease However, statements are often so inaccurate that a differential diagnosis of intestinal disorders cannot be made from the history which has been revealed by the patient Because of these factors, proctoscopic examination is indispensable

There is a certain order which should be followed in examining such a patient Stools should be examined first This is done primarily to find out if parasites or ova are present and if there is any evidence of blood If the proctoscopic examination is done previous to examination of the stool, the blood may be attributable to trauma The digital examination should, of course, always be carefully made previous to any other investigation, and if a lesion is discovered it is not often necessary to examine the stools I recall instances in which amebiasis has coexisted with carcinoma of the rectum or sigmoid Digital examination alone is insufficient Often a benign lesion in the midst of an indurated, inflammatory mass which has fixed the walls of the rectum in the pelvis may feel like a carcinoma It may be difficult even by direct visual examination, to differentiate such a growth from one which is malignant Of course, we have recourse to the use of the microscope However, many times one will take several sections from a carcinoma before one will succeed in discovering malignant tissue How then is one to be certain about the diagnosis? If a lesion looks malignant, and the first specimen taken is reported to be benign, we take other specimens until we are convinced that no malignancy exists in the deeper portions of the lesions

We have seen instances, however, in which it was difficult

to ascertain that a growth was not malignant, in spite of numerous reports that the tissue was not malignant. There have been instances in which it was necessary to remove the entire rectum because of ulceration and deformity. On several occasions, thorough microscopic examination following removal of the rectum failed to disclose evidence of malignancy. On the other hand, we have seen cases in which the rectum was removed and microscopic study proved that the lesion was carcinoma in spite of the fact that no carcinomatous tissue was seen in the sections removed before the operation was performed.

This is the part played by the diagnostician, the proctologist and the roentgenologist in the cooperative management in cases of carcinoma of the colon From the investigations outlined, the operability of the growth is determined By proctoscopic examination it is possible to get definite information concerning the size and mobility of the growth, and the amount of obstruction caused by it Its position and the other structures involved usually can be determined A lesion which is annular and freely movable, and which is situated high in the sigmoid, above the reflection of the peritoneum, may be suitable for obstructive resection If such a growth is in the region of the rectosigmoid it may be desirable to resect it and to anastomose the ends of the bowel over a tube Slight variations might indicate an abdominoperineal type of operation or a posterior resection The grade of malignancy is a very important factor in determining operability All such questions are answered insofar as possible during these investigations and when the patient arrives in the hospital he is ready for the preoperative preparation which consists of certain dietetic and eliminative features, along with preoperative vaccination against peritonitis When the patient comes to operation, all available information is at hand and all preoperative arrangements have been completed

Medical Clinics of North America
September 1935 Mayo Clinic Number

COOPERATIVE MANAGEMENT IN CASES OF CARCINOMA OF THE COLON THE SURGEON'S VIEW

CHARLES W MAYO

I do not believe that there has been any advance in the treatment of carcinoma of the colon which is comparable to the development of the cooperative management in handling these cases the diagnostician, proctologist, anesthetist, and surgeon work together in this cooperative management Each patient who is to submit to a colonic operation, of course is prepared in approximately the same way If the multiple-stage operation is to be done that is colostomy and later posterior resection the combined abdominoperineal operation or ileocolostomy and then resection of the right colon, the same type of preparation is employed for each of these surgical procedures

section of the rectum because they and we did not trust radium or fulguration No evidence of carcinoma was found in a few at the time of the posterior resection A certain percentage of cases, in which the growth is polypoid, or on the lateral or posterior wall of the rectum, has been treated successfully with radium or fulguration if metastasis has not occurred

If the growth is on the anterior wall of the rectum, or has spread to prostate, urethra, or bladder, it is necessary to do a more radical procedure, such as a colostomy and posterior resection in two stages or in some instances a combined abdominoperineal operation It is very important to consider well this matter of combined abdominoperineal resection I think it is of particular value to know that it is done with much more safety in a case in which the patient is rather thin and not too old After making the colostomy, if the patient is a man, it usually is best to turn him over on the table and complete the resection by the posterior route However, if the patient is a woman and a good dissection of the rectum can be done from above, I think one saves time by performing the complete operation with the patient on her back in the lithotomy position Some surgeons do both sexes thus The English surgeons for the most part do the posterior resection with the patient on the side The operation sometimes has been done by two surgeons in order to save time One hour, or even longer, is not too long to have a patient on the table Dry heat is applied to the wound and some kind of antiseptic solution is employed if necessary In posterior wounds the packs should be removed by the fifth day after operation, e wound should be irrigated with a rubber tube and syringe - pack comes out easily if it has been soaked twice a day or two or three days before its removal If it is painful, some morphine or intravenous anesthetic may be administered

There is one point I should like to stress in regard to preoperative preparation by introduction of intraperitoneal vaccine It increases the intraperitoneal cellular count on an average of fourteen and a half times, changes the cells to the

phylactic type and affords additional protection against infection In considering the value of intraperitoneal vaccine, three divisions of operative cases should be made the first, in which little if any soiling has occurred the second, in which marked soiling has occurred from whatever cause, and a middle group, in which moderate soiling has been unavoidable Intraperitoneal vaccine is of value only in two of these groups, and the balance between life and death is swung on the side of life in a small percentage by the additional marshalling of police forces It does not prevent peritonitis and no amount of the vaccine can save the patient with gross soiling of the abdominal cavity We feel that it has been of definite value

CUMULATIVE INDEX

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